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(54) **4'-THIO-NUCLEOTIDE AND -NUCLEOSIDE PRODRUGS FOR THE TREATMENT OF CANCER**

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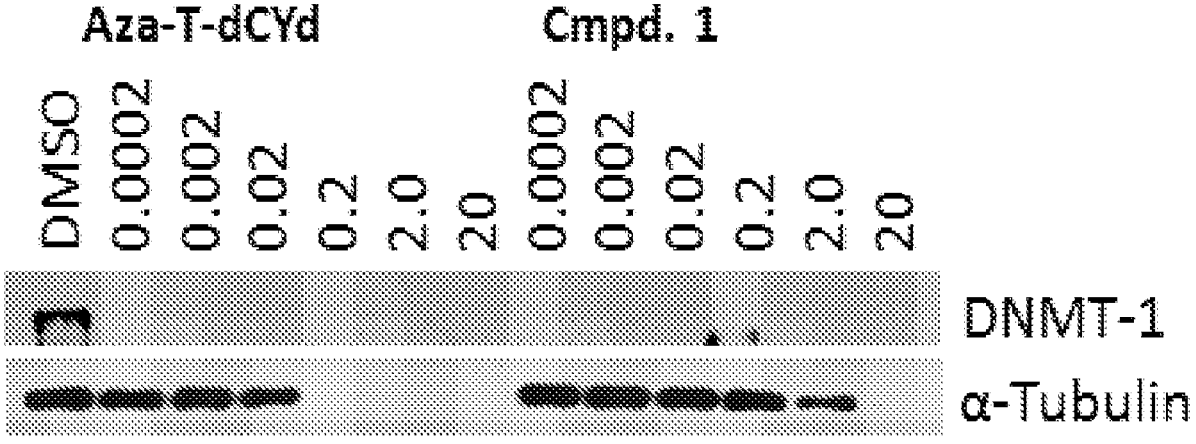
CPC ***C07H 19/12*** (2013.01); ***A61P 35/00*** (2018.01); ***C07H 19/10*** (2013.01); ***C07H 19/06*** (2013.01)

(57) **ABSTRACT**

The present disclosure is concerned with 4'-thio nucleotide and nucleoside compounds for the treatment of various cancers such as, for example, sarcomas, carcinomas, hematological cancers, solid tumors, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanomas, gliomas, leukemias, lymphomas, chronic myeloproliferative disorders, myelodysplastic syndromes, myeloproliferative neoplasms, and plasma cell neoplasms (myelomas). This abstract is intended as a scanning tool for purposes of searching in the particular art and is not intended to be limiting of the present invention.



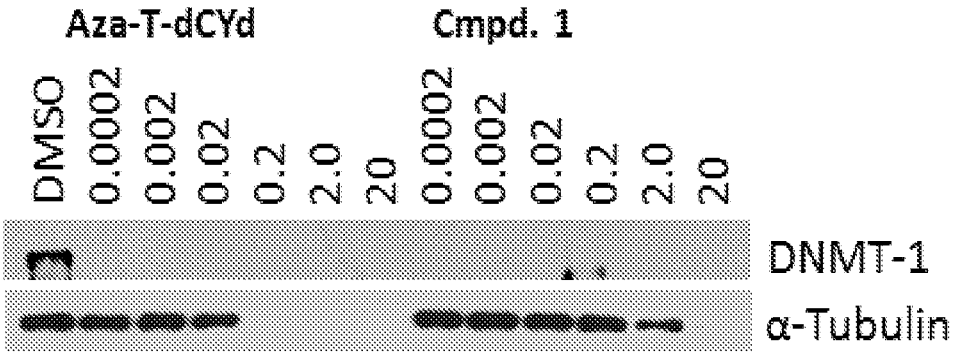

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FIG. 1A

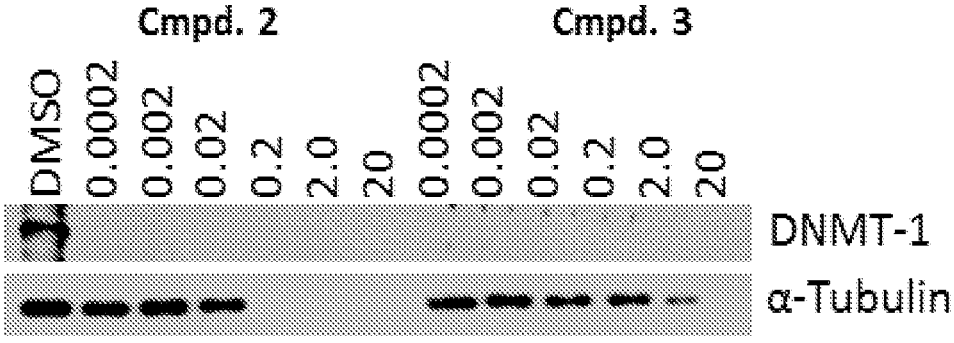
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FIG. 1B

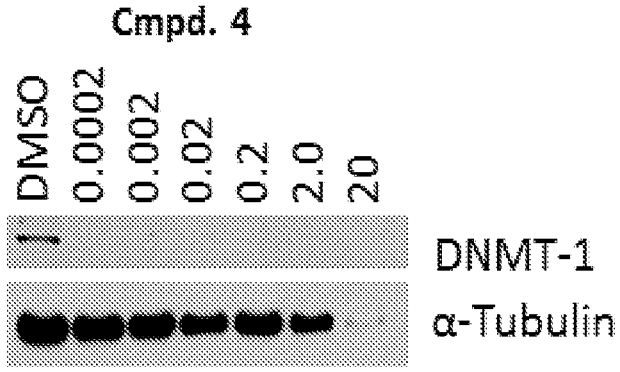
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FIG. 1C

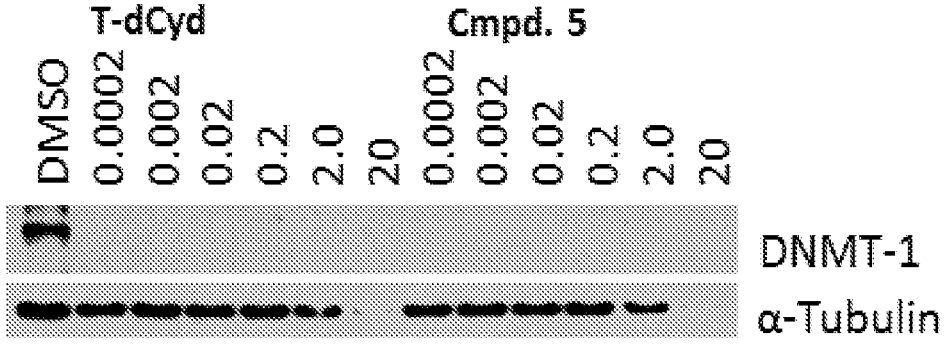
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FIG. 1D

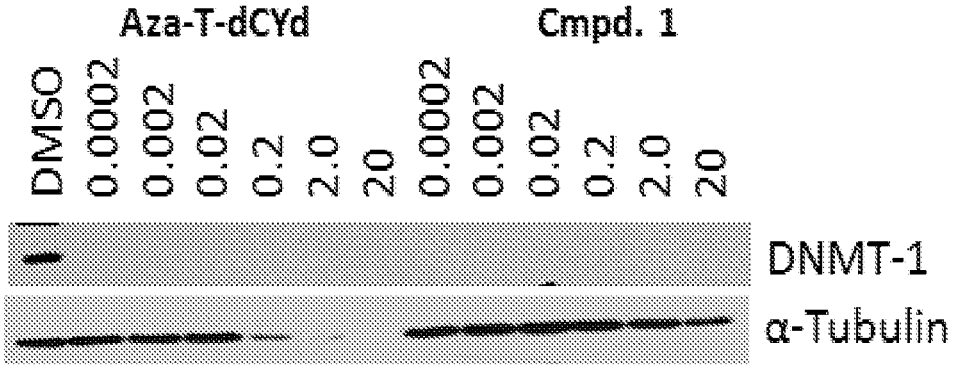
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FIG. 2A

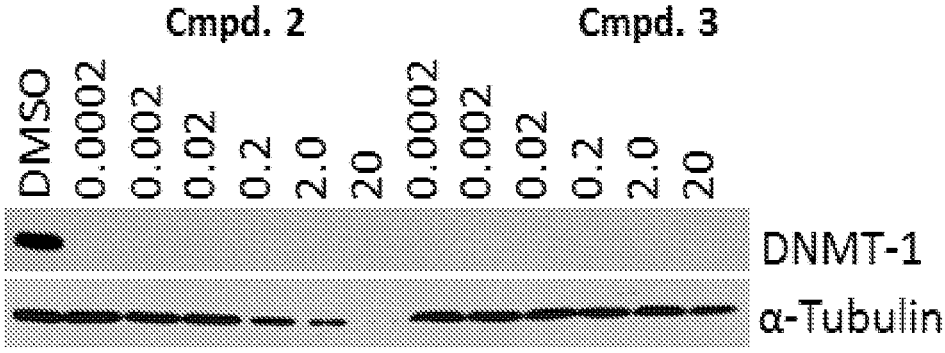
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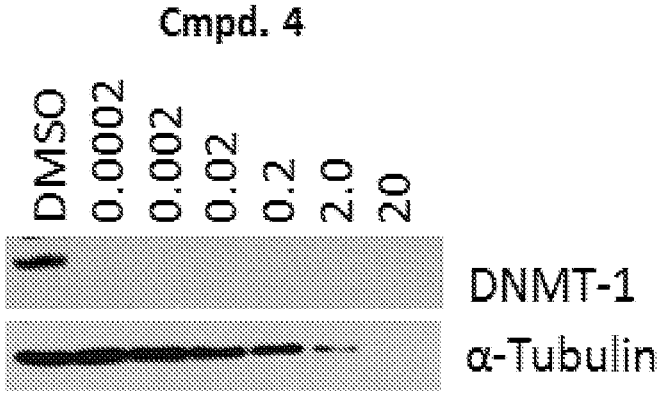
FIG. 2B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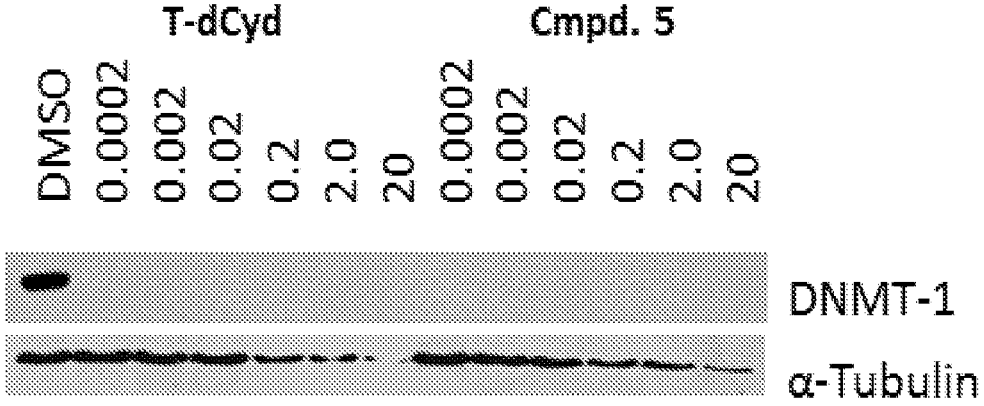
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FIG. 2D

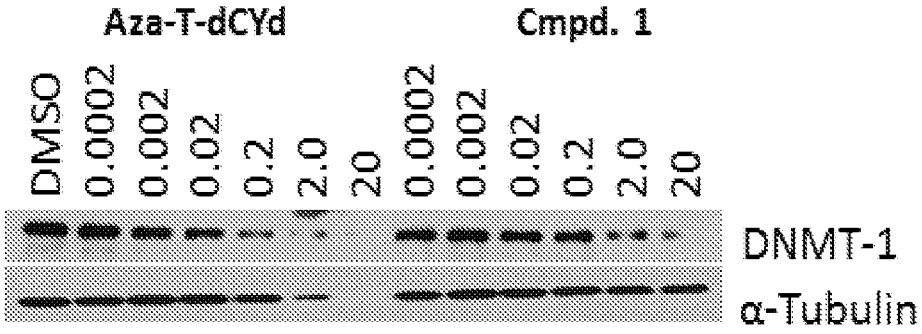
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FIG. 3A

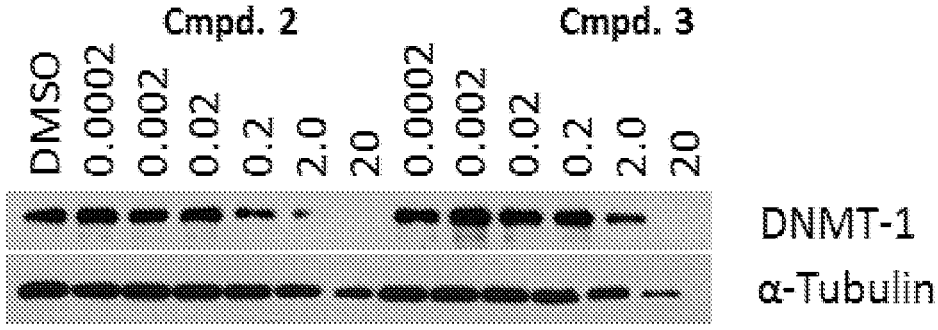
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FIG. 3B

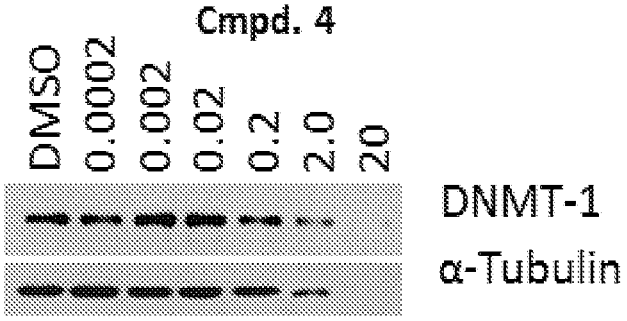
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FIG. 3C

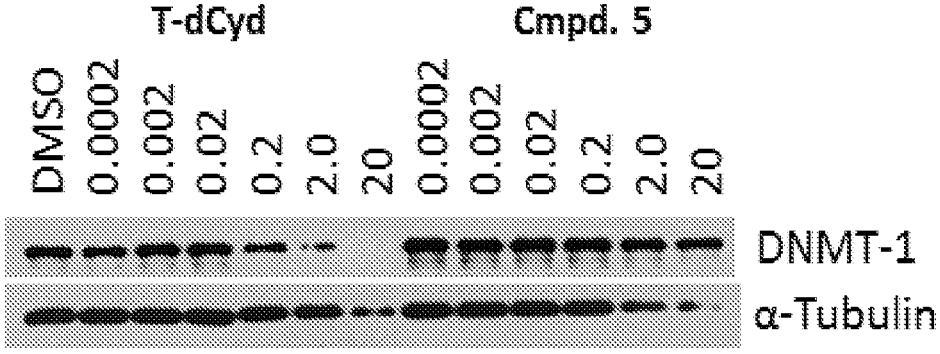
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FIG. 3D

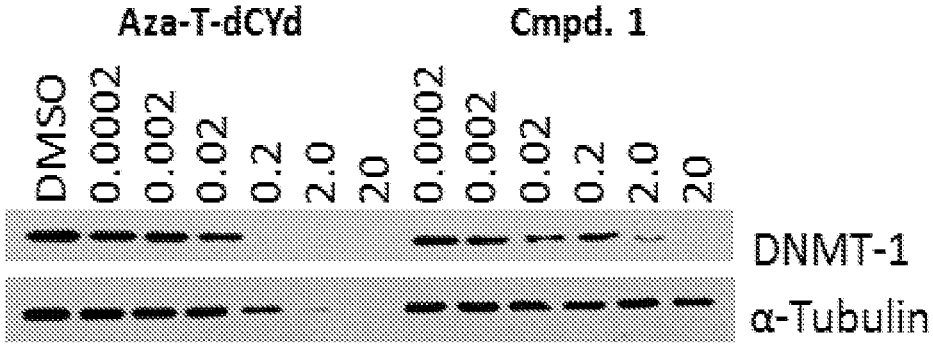
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FIG. 4A

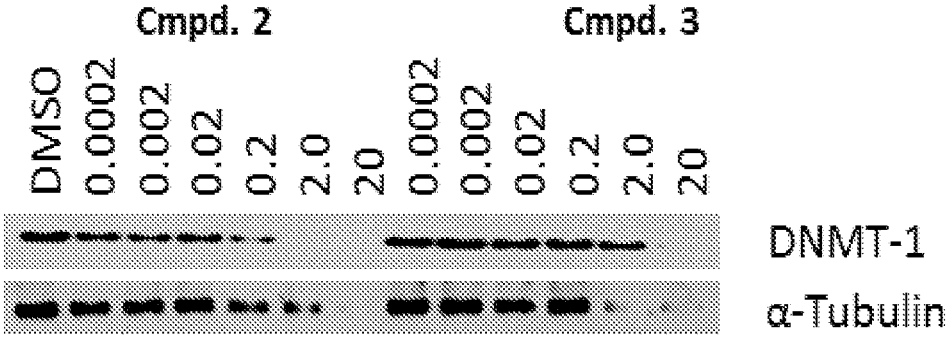
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FIG. 4B

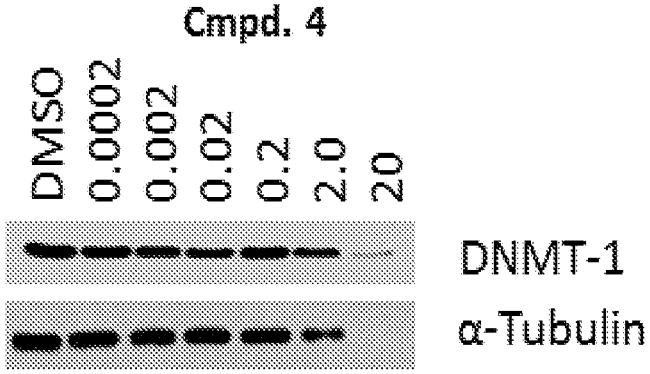
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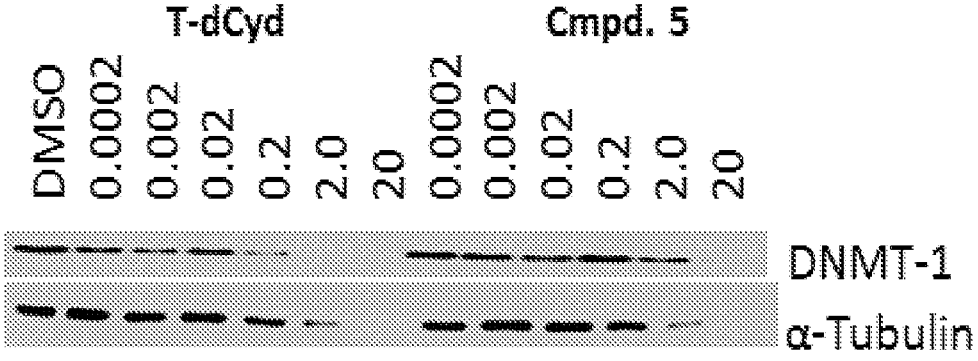
FIG. 4C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α-Tubulin

FIG. 4D

4'-THIO-NUCLEOTIDE AND -NUCLEOSIDE PRODRUGS FOR THE TREATMENT OF CANCER

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Application No. 62/660,208, filed on Apr. 19, 2018, which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Cancer is a disease characterized primarily by an uncontrolled division of abnormal cells derived from a given normal tissue and the invasion of adjacent tissues by these malignant cells. Blood or lymphatic transportation can spread cancer cells to other parts of the body leading to regional lymph nodes and to distant sites (metastasis). Cancer is a complex, multistep process that begins with minor preneoplastic changes, which may under certain conditions progress to neoplasia. There are more than 100 different types of cancer, which can be grouped into broader categories. The main categories include: carcinoma, sarcoma, leukemia, lymphoma and myeloma, and central nervous system cancers. The incidence of cancer continues to climb as the general population ages, as new cancers develop, and as susceptible populations (e.g., people infected with AIDS or excessively exposed to sunlight) grow. A tremendous demand therefore exists for new methods and compositions that can be used to treat patients with cancer.

[0003] Hematologic or hematopoietic malignancies are cancers of the blood or bone marrow, including leukemia and lymphoma. Leukemia is a type of cancer of the blood characterized by abnormal accumulation of immature white blood cells. There are four types of leukemia: acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML). Acute leukemia is a rapidly progressing disease that results in the accumulation of immature, functionless cells in the marrow and blood. The marrow often stops producing enough normal red cells, which include cells and platelets. On the other hand, chronic leukemia progresses more slowly and allows greater numbers of more mature, functional cells to be made.

[0004] Leukemia can affect people at any age. The cause of most cases of leukemia is not known. Extraordinary doses of radiation and certain cancer therapies are possible causes. About 90% of leukemia cases are diagnosed in adults. Cases of chronic leukemia account for 4.5 percent more cases that acute leukemia. The most common types of leukemia in adults are acute myelogenous leukemia (AML), with estimated 14,590 new cases in 2013, and chronic lymphocytic leukemia (CLL), with about 15,680 new cases in 2013. Chronic myelogenous leukemia (CML) was estimated to affect about 5,920 persons in 2013 (data from the Leukemia and Lymphoma Society, *Facts* 2013, August 2013).

[0005] The dramatic improvement in blood cancer treatment in the latter part of the 20th century is largely the result of chemotherapy. In addition, there are more than 50 drugs individually used to treat these disorders and a number of potential new therapies are under investigation in clinical trials. While current chemotherapy can result in complete remissions, the long-term, disease-free survival rate for leukemia, in particular AML, is low. For example, the overall relative survival rate for AML was estimated to be about 59% from 2003 to 2009. Therefore, there is a clear and unmet need for effective therapeutics for treatment of blood cancers, including leukemia.

[0006] Treatment options for hepatocellular carcinoma have been limited, especially in the case of advanced or recurrent hepatocellular carcinoma. Surgery and radiation therapy are options for early stage liver cancer, but not very effective for advanced or recurrent hepatocellular carcinoma. Systematic chemotherapies have not been particularly effective, and there are a very limited number of drugs available for use. The recently approved kinase inhibitor sorafenib has been shown to be effective in treating hepatocellular carcinoma. However, it can slow or stop advanced liver cancer from progressing for only a few months longer than without treatment.

[0007] In human cancer, the DNA methylation pattern becomes aberrant, resulting in hypermethylation and transcriptional silencing of the promoters of a number of tumor supporessor genes. Thus, restoring the expression of hypermethylated tumor suppressor genes by inhibiting the DNA methyltransferases (DNMT1, DNMT3A, and DNMT3B) has emerged as a desirable strategy against cancer. To date, demethylating agents such as azacytidine and decitabine have been used clinically in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) and experimentally in some forms of solid tumors. However, expansion of these compounds to solid tumor applications (e.g., bladder, ovarian, and colorectal cancers) remains limited by their pharmacokinetic profiles.

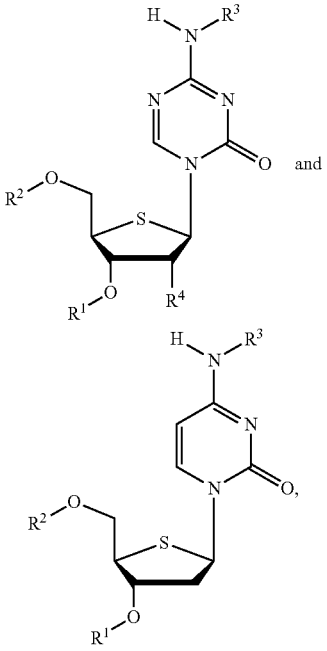
[0008] New therapies for the treatment of prevention of cancer are needed.

[0009] In sum, despite the widespread prevalence of cancer, current treatments continue to suffer from a range of drawbacks. Thus, there remains a need for compounds and compositions for the treatment of cancer and methods of making and using same.

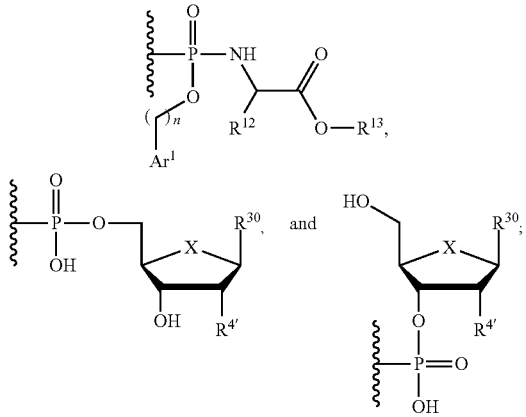
SUMMARY

[0010] In accordance with the purpose(s) of the invention, as embodied and broadly described herein, the invention, in one aspect, relates to compounds and compositions for use in the prevention and treatment of disorders of uncontrolled cellular proliferation such as, for example, cancers including, but not limited to, sarcomas, carcinomas, hematological cancers, solid tumors, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanomas, gliomas, leukemias, lymphomas, chronic myeloproliferative disorders, myelodysplastic syndromes, myeloproliferative neoplasms, and plasma cell neoplasms (myelomas).

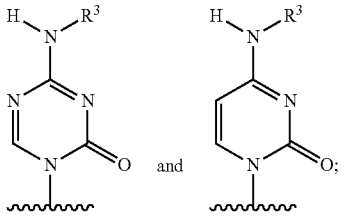
[0011] Disclosed are compounds having a structure represented by a formula selected from:



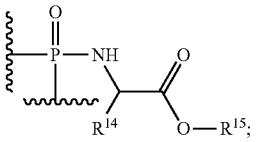
wherein each of R^1 and R^2 is independently selected from hydrogen, —C(O)R^{10}, —P(O)(OR^{11})$_2$, —P(O)(OH)OP(O)(OH)OP(O)(OH)$_2$, and a structure represented by a formula selected from:



provided that one of R^1 and R^2 is hydrogen; wherein n is selected from 0, 1, and 2; wherein X, when present, is selected from O and S; wherein R^{10}, when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and —CH(NH_2)R^{20}; wherein R^{20}, when present, is selected from hydrogen, methyl, isopropyl, isobutyl, sec-butyl, —(CH_2)$_3$NHC(NH)NH_2, —(CH_2)$_4$NH_2, —CH_2CO_2H, —(CH_2)$_2$CO_2H, —CH_2OH, —CH(OH)CH_3, —CH_2C(O)NH_2, —(CH_2)$_2$C(O)NH_2, —CH_2SH, —(CH_2)$_2$SCH_3, —CH_2SeH, —CH_2C$_6$H$_5$, and —CH_2Cy^1; wherein Cy^1, when present, is selected from monocylic aryl, para-hydroxy monocyclic aryl, 4-imidazolyl, and 3-indolyl; wherein each occurrence of RH, when present, is independently selected from hydrogen, —(C1-C10 alkyl)CO_2(C1-C10 alkyl), (C1-C10 alkoxy)CO_2(C1-C10 alkyl), —(C1-C10 alkyl)CO_2(C1-C10 alkylthio), —(C1-C10 alkyl)-S—S—(C1-C10 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and OH; wherein Ar^2, when present, is selected from aryl and heteroaryl substituted with 1 or 2 groups independently selected from C1-C10 alkyl and nitro; wherein R^{12}, when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylamino, (C1-C8)C(O)NH_2, aryl, and —(CH_2)aryl; wherein R^{13}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar^3; wherein Ar^3, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino; wherein Ar^1, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino; wherein R^{30}, when present, is a structure selected from:

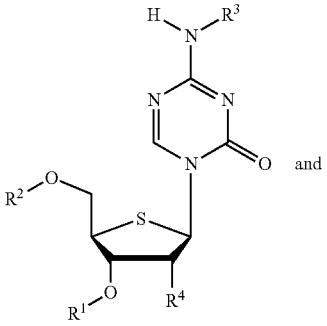


wherein R^{31}, when present, is selected from hydrogen, —C(O)(C1-C30 alkyl), and —C(O)(C2-C30 alkenyl); or wherein each of R^1 and R^2 together comprise a structure represented by a formula:



wherein R^{14}, when present, is C1-C8 alkyl; wherein R^{15}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and aryl substituted with 0 or 1 C1-C10 alkyl groups; wherein R^3 is selected from hydrogen, —C(O)(C1-C30 alkyl), and —C(O)(C2-C30 alkenyl); wherein each of R^4 and $R^{4'}$, when present, is independently selected from hydrogen, fluoro, —CN, C2-C4 alkenyl, C2-C4 alkynyl, C1-C4 haloalkyl, and —OR^{16}; and wherein R^{16}, when present, is selected from hydrogen, methyl, and —C(O)R^{10}, provided that R^1, R^2, and R^3 are not simultaneously hydrogen, or a pharmaceutically acceptable salt thereof.

[0012] Also disclosed are compounds having a structure represented by a formula selected from:



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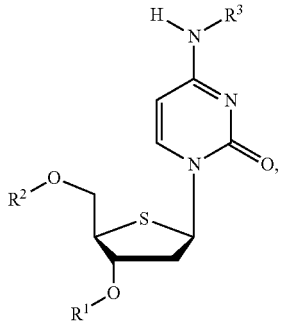
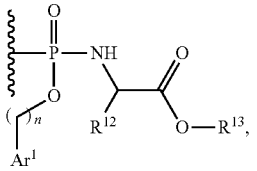
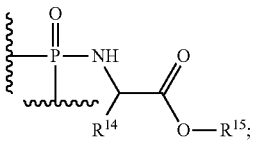


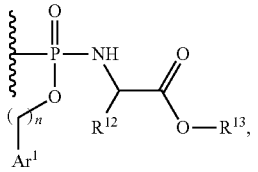
wherein each of R^1 and R^2 is independently selected from hydrogen, —C(O)R^{10}, —P(O)(OR^{11})$_2$, and a structure represented by a formula:



provided that one of R^1 and R^2 is hydrogen; wherein n is selected from 0, 1, and 2; wherein R^{10}, when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and —CH(NH_2)R^{20}; wherein R^{20}, when present, is selected from hydrogen, methyl, isopropyl, isobutyl, sec-butyl, —(CH_2)$_3$NHC(NH)NH_2, —(CH_2)$_4NH_2$, —CH_2CO_2H, —(CH_2)$_2CO_2H$, —CH_2OH, —CH(OH)CH_3, —$CH_2C(O)NH_2$, —(CH_2)$_2C(O)NH_2$, —CH_2SH, —(CH_2)$_2SCH_3$, —CH_2SeH, —$CH_2C_6H_5$, and —CH_2Cy^1; wherein Cy^1, when present, is selected from monocylic aryl, para-hydroxy monocyclic aryl, 4-imidazolyl, and 3-indolyl; wherein each occurrence of R^{11}, when present, is independently selected from hydrogen, —(C1-C10 alkyl)CO_2(C1-C10 alkyl), —(C1-C10 alkoxy)CO_2(C1-C10 alkyl), —(C1-C10 alkyl)CO_2(C1-C10 alkylthio), —(C1-C10 alkyl)-S—S—(C1-C10 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and OH; wherein Ar^2, when present, is selected from aryl and heteroaryl substituted with 1 or 2 groups independently selected from C1-C10 alkyl and nitro; wherein R^{12}, when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylamino, —(C1-C8)C(O)NH_2, aryl, and —(CH_2)aryl; wherein R^{13}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and aryl substituted with 0 or 1 C1-C10 alkyl group; wherein Ar^1, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino; or wherein each of R^1 and R^2 together comprise a structure represented by a formula:



wherein R^{14}, when present, is C1-C8 alkyl; wherein R^{15}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and aryl substituted with 0 or 1 C1-C10 alkyl groups; wherein R^3 is selected from hydrogen, fluoro, —C(O)(C1-C30 alkyl), and —C(O)(C2-C30 alkenyl); wherein R^4, when present, is selected from hydrogen, fluoro, and —OR^{16}; and wherein R^{16}, when present, is selected from hydrogen, methyl, —C(O)R^{10}, —P(O)(OR^{11})$_2$, and a structure represented by a formula:



provided that R^1, R^2, and R^3 are not simultaneously hydrogen, or a pharmaceutically acceptable salt thereof.

[0013] Also disclosed are pharmaceutical compositions comprising a therapeutically effective amount of a disclosed compound and a pharmaceutically acceptable carrier.

[0014] Also disclosed are methods of treating a disorder of uncontrolled cellular proliferation in a subject, the method comprising the step of administering to the subject an effective amount of a disclosed compound.

[0015] Also disclosed are kits comprising a disclosed compound, and one or more of: (a) at least one agent associated with the treatment of a disorder of uncontrolled cellular proliferation; (b) instructions for administering the compound in connection with treating a disorder of uncontrolled cellular proliferation; and (c) instructions for treating a disorder of uncontrolled cellular proliferation.

[0016] While aspects of the present invention can be described and claimed in a particular statutory class, such as the system statutory class, this is for convenience only and one of skill in the art will understand that each aspect of the present invention can be described and claimed in any statutory class. Unless otherwise expressly stated, it is in no way intended that any method or aspect set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not specifically state in the claims or descriptions that the steps are to be limited to a specific order, it is in no way intended

that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, or the number or type of aspects described in the specification.

BRIEF DESCRIPTION OF THE FIGURES

[0017] The accompanying figures, which are incorporated in and constitute a part of this specification, illustrate several aspects and together with the description serve to explain the principles of the invention.

[0018] FIG. **1**A-D shows representative data demonstrating depletion of DNMT-1 in NCI-H23 cells by Aza-T-dCYd, T-dCyd, and compound nos. 1-5 for 96 hours.

[0019] FIG. **2**A-D shows representative data demonstrating depletion of DNMT-1 in NCI-H23 cells by Aza-T-dCYd, T-dCyd, and compound nos. 1-5 for 96 hours.

[0020] FIG. **3**A-D shows representative data demonstrating depletion of DNMT-1 in NCI-H23 cells by Aza-T-dCYd, T-dCyd, and compound nos. 1-5 for 96 hours.

[0021] FIG. **4**A-D shows representative data demonstrating depletion of DNMT-1 in NCI-H23 cells by Aza-T-dCYd, T-dCyd, and compound nos. 1-5 for 96 hours.

[0022] Additional advantages of the invention will be set forth in part in the description, which follows, and in part will be obvious from the description, or can be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DETAILED DESCRIPTION

[0023] The present invention can be understood more readily by reference to the following detailed description of the invention and the Examples included therein.

[0024] Before the present compounds, compositions, articles, systems, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, example methods and materials are now described.

[0025] While aspects of the present invention can be described and claimed in a particular statutory class, such as the system statutory class, this is for convenience only and one of skill in the art will understand that each aspect of the present invention can be described and claimed in any statutory class. Unless otherwise expressly stated, it is in no way intended that any method or aspect set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not specifically state in the claims or descriptions that the steps are to be limited to a specific order, it is in no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, or the number or type of aspects described in the specification.

[0026] Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this pertains. The references disclosed are also individually and specifically incorporated by reference herein for the material contained in them that is discussed in the sentence in which the reference is relied upon. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided herein may be different from the actual publication dates, which can require independent confirmation.

A. Definitions

[0027] As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a functional group," "an alkyl," or "a residue" includes mixtures of two or more such functional groups, alkyls, or residues, and the like.

[0028] As used in the specification and in the claims, the term "comprising" can include the aspects "consisting of" and "consisting essentially of."

[0029] Ranges can be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms another aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

[0030] As used herein, the terms "about" and "at or about" mean that the amount or value in question can be the value designated some other value approximately or about the same. It is generally understood, as used herein, that it is the nominal value indicated ±10% variation unless otherwise indicated or inferred. The term is intended to convey that similar values promote equivalent results or effects recited in the claims. That is, it is understood that amounts, sizes, formulations, parameters, and other quantities and characteristics are not and need not be exact, but can be approximate and/or larger or smaller, as desired, reflecting tolerances, conversion factors, rounding off, measurement error and the like, and other factors known to those of skill in the art. In general, an amount, size, formulation, parameter or other quantity or characteristic is "about" or "approximate" whether or not expressly stated to be such. It is understood that where "about" is used before a quantitative value, the

parameter also includes the specific quantitative value itself, unless specifically stated otherwise.

[0031] References in the specification and concluding claims to parts by weight of a particular element or component in a composition denotes the weight relationship between the element or component and any other elements or components in the composition or article for which a part by weight is expressed. Thus, in a compound containing 2 parts by weight of component X and 5 parts by weight component Y, X and Y are present at a weight ratio of 2:5, and are present in such ratio regardless of whether additional components are contained in the compound.

[0032] A weight percent (wt. %) of a component, unless specifically stated to the contrary, is based on the total weight of the formulation or composition in which the component is included.

[0033] As used herein, "IC_{50}" is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50% inhibition of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc. In one aspect, an IC_{50} can refer to the concentration of a substance that is required for 50% inhibition in vivo, as further defined elsewhere herein. In a further aspect, IC_{50} refers to the half-maximal (50%) inhibitory concentration (IC) of a substance.

[0034] As used herein, "EC_{50}" is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50% agonism of a biological process, or component of a process, including a protein, subunit, organelle, ribonucleoprotein, etc. In one aspect, an EC_{50} can refer to the concentration of a substance that is required for 50% agonism in vivo, as further defined elsewhere herein. In a further aspect, EC_{50} refers to the concentration of agonist that provokes a response halfway between the baseline and maximum response.

[0035] As used herein, the terms "optional" or "optionally" means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

[0036] As used herein, the term "subject" can be a vertebrate, such as a mammal, a fish, a bird, a reptile, or an amphibian. Thus, the subject of the herein disclosed methods can be a human, non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig or rodent. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered. In one aspect, the subject is a mammal A patient refers to a subject afflicted with a disease or disorder. The term "patient" includes human and veterinary subjects.

[0037] As used herein, the term "treatment" refers to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder. In various aspects, the term covers any treatment of a subject, including a mammal (e.g., a human), and includes: (i) preventing the disease from occurring in a subject that can be predisposed to the disease but has not yet been diagnosed as having it; (ii) inhibiting the disease, i.e., arresting its development; or (iii) relieving the disease, i.e., causing regression of the disease. In one aspect, the subject is a mammal such as a primate, and, in a further aspect, the subject is a human. The term "subject" also includes domesticated animals (e.g., cats, dogs, etc.), livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), and laboratory animals (e.g., mouse, rabbit, rat, guinea pig, fruit fly, etc.).

[0038] As used herein, the term "prevent" or "preventing" refers to precluding, averting, obviating, forestalling, stopping, or hindering something from happening, especially by advance action. It is understood that where reduce, inhibit or prevent are used herein, unless specifically indicated otherwise, the use of the other two words is also expressly disclosed.

[0039] As used herein, the term "diagnosed" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by the compounds, compositions, or methods disclosed herein.

[0040] As used herein, the terms "administering" and "administration" refer to any method of providing a pharmaceutical preparation to a subject. Such methods are well known to those skilled in the art and include, but are not limited to, oral administration, transdermal administration, administration by inhalation, nasal administration, topical administration, intravaginal administration, ophthalmic administration, intraaural administration, intracerebral administration, rectal administration, sublingual administration, buccal administration, and parenteral administration, including injectable such as intravenous administration, intra-arterial administration, intramuscular administration, and subcutaneous administration. Administration can be continuous or intermittent. In various aspects, a preparation can be administered therapeutically; that is, administered to treat an existing disease or condition. In further various aspects, a preparation can be administered prophylactically; that is, administered for prevention of a disease or condition.

[0041] As used herein, the terms "effective amount" and "amount effective" refer to an amount that is sufficient to achieve the desired result or to have an effect on an undesired condition. For example, a "therapeutically effective amount" refers to an amount that is sufficient to achieve the desired therapeutic result or to have an effect on undesired symptoms, but is generally insufficient to cause adverse side effects. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed and like factors well known in the medical arts. For example, it is well within the

skill of the art to start doses of a compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the effective daily dose can be divided into multiple doses for purposes of administration. Consequently, single dose compositions can contain such amounts or submultiples thereof to make up the daily dose. The dosage can be adjusted by the individual physician in the event of any contraindications. Dosage can vary, and can be administered in one or more dose administrations daily, for one or several days. Guidance can be found in the literature for appropriate dosages for given classes of pharmaceutical products. In further various aspects, a preparation can be administered in a "prophylactically effective amount," that is, an amount effective for prevention of a disease or condition.

[0042] As used herein, "dosage form" means a pharmacologically active material in a medium, carrier, vehicle, or device suitable for administration to a subject. A dosage forms can comprise inventive a disclosed compound, a product of a disclosed method of making, or a salt, solvate, or polymorph thereof, in combination with a pharmaceutically acceptable excipient, such as a preservative, buffer, saline, or phosphate buffered saline. Dosage forms can be made using conventional pharmaceutical manufacturing and compounding techniques. Dosage forms can comprise inorganic or organic buffers (e.g., sodium or potassium salts of phosphate, carbonate, acetate, or citrate) and pH adjustment agents (e.g., hydrochloric acid, sodium or potassium hydroxide, salts of citrate or acetate, amino acids and their salts) antioxidants (e.g., ascorbic acid, alpha-tocopherol), surfactants (e.g., polysorbate 20, polysorbate 80, polyoxyethylene9-10 nonyl phenol, sodium desoxycholate), solution and/or cryo/lyo stabilizers (e.g., sucrose, lactose, mannitol, trehalose), osmotic adjustment agents (e.g., salts or sugars), antibacterial agents (e.g., benzoic acid, phenol, gentamicin), antifoaming agents (e.g., polydimethylsilozone), preservatives (e.g., thimerosal, 2-phenoxyethanol, EDTA), polymeric stabilizers and viscosity-adjustment agents (e.g., polyvinylpyrrolidone, poloxamer 488, carboxymethylcellulose) and co-solvents (e.g., glycerol, polyethylene glycol, ethanol). A dosage form formulated for injectable use can have a disclosed compound, a product of a disclosed method of making, or a salt, solvate, or polymorph thereof, suspended in sterile saline solution for injection together with a preservative.

[0043] As used herein, "kit" means a collection of at least two components constituting the kit. Together, the components constitute a functional unit for a given purpose. Individual member components may be physically packaged together or separately. For example, a kit comprising an instruction for using the kit may or may not physically include the instruction with other individual member components. Instead, the instruction can be supplied as a separate member component, either in a paper form or an electronic form which may be supplied on computer readable memory device or downloaded from an internet website, or as recorded presentation.

[0044] As used herein, "instruction(s)" means documents describing relevant materials or methodologies pertaining to a kit. These materials may include any combination of the following: background information, list of components and their availability information (purchase information, etc.), brief or detailed protocols for using the kit, trouble-shooting, references, technical support, and any other related documents. Instructions can be supplied with the kit or as a separate member component, either as a paper form or an electronic form, which may be supplied on computer readable memory device or downloaded from an internet website, or as recorded presentation. Instructions can comprise one or multiple documents, and are meant to include future updates.

[0045] As used herein, the terms "therapeutic agent" include any synthetic or naturally occurring biologically active compound or composition of matter which, when administered to an organism (human or nonhuman animal), induces a desired pharmacologic, immunogenic, and/or physiologic effect by local and/or systemic action. The term therefore encompasses those compounds or chemicals traditionally regarded as drugs, vaccines, and biopharmaceuticals including molecules such as proteins, peptides, hormones, nucleic acids, gene constructs and the like. Examples of therapeutic agents are described in well-known literature references such as the Merck Index (14th edition), the Physicians' Desk Reference (64th edition), and The Pharmacological Basis of Therapeutics (12th edition), and they include, without limitation, medicaments; vitamins; mineral supplements; substances used for the treatment, prevention, diagnosis, cure or mitigation of a disease or illness; substances that affect the structure or function of the body, or pro-drugs, which become biologically active or more active after they have been placed in a physiological environment. For example, the term "therapeutic agent" includes compounds or compositions for use in all of the major therapeutic areas including, but not limited to, adjuvants; anti-infectives such as antibiotics and antiviral agents; anticancer and anti-neoplastic agents such as kinase inhibitors, poly ADP ribose polymerase (PARP) inhibitors and other DNA damage response modifiers, epigenetic agents such as bromodomain and extra-terminal (BET) inhibitors, histone deacetylase (HDAc) inhibitors, iron chelotors and other ribonucleotides reductase inhibitors, proteasome inhibitors and Nedd8-activating enzyme (NAE) inhibitors, mammalian target of rapamycin (mTOR) inhibitors, traditional cytotoxic agents such as paclitaxel, dox, irinotecan, and platinum compounds, immune checkpoint blockade agents such as cytotoxic T lymphocyte antigen-4 (CTLA-4) monoclonal antibody (mAB), programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) mAB, cluster of differentiation 47 (CD47) mAB, toll-like receptor (TLR) agonists and other immune modifiers, cell therapeutics such as chimeric antigen receptor T-cell (CAR-T)/chimeric antigen receptor natural killer (CAR-NK) cells, and proteins such as interferons (IFNs), interleukins (ILs), and mAbs; anti-ALS agents such as entry inhibitors, fusion inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors, NCP7 inhibitors, protease inhibitors, and integrase inhibitors; analgesics and analgesic combinations, anorexics, anti-inflammatory agents, anti-epileptics, local and general anesthetics, hypnotics, sedatives, antipsychotic agents, neuroleptic agents, antidepressants, anxiolytics, antagonists, neuron blocking agents, anticholinergic and cholinomimetic agents, antimuscarinic and muscarinic agents, antiadrenergics, antiarrhythmics, antihypertensive agents, hormones, and nutrients, antiarthritics, antiasthmatic agents, anticonvulsants, antihistamines, antinauseants, antineoplastics, antipruritics,

antipyretics; antispasmodics, cardiovascular preparations (including calcium channel blockers, beta-blockers, beta-agonists and antiarrythmics), antihypertensives, diuretics, vasodilators; central nervous system stimulants; cough and cold preparations; decongestants; diagnostics; hormones; bone growth stimulants and bone resorption inhibitors; immunosuppressives; muscle relaxants; psychostimulants; sedatives; tranquilizers; proteins, peptides, and fragments thereof (whether naturally occurring, chemically synthesized or recombinantly produced); and nucleic acid molecules (polymeric forms of two or more nucleotides, either ribonucleotides (RNA) or deoxyribonucleotides (DNA) including both double- and single-stranded molecules, gene constructs, expression vectors, antisense molecules and the like), small molecules (e.g., doxorubicin) and other biologically active macromolecules such as, for example, proteins and enzymes. The agent may be a biologically active agent used in medical, including veterinary, applications and in agriculture, such as with plants, as well as other areas. The term "therapeutic agent" also includes without limitation, medicaments; vitamins; mineral supplements; substances used for the treatment, prevention, diagnosis, cure or mitigation of disease or illness; or substances which affect the structure or function of the body; or pro-drugs, which become biologically active or more active after they have been placed in a predetermined physiological environment.

[0046] The term "pharmaceutically acceptable" describes a material that is not biologically or otherwise undesirable, i.e., without causing an unacceptable level of undesirable biological effects or interacting in a deleterious manner.

[0047] As used herein, the term "derivative" refers to a compound having a structure derived from the structure of a parent compound (e.g., a compound disclosed herein) and whose structure is sufficiently similar to those disclosed herein and based upon that similarity, would be expected by one skilled in the art to exhibit the same or similar activities and utilities as the claimed compounds, or to induce, as a precursor, the same or similar activities and utilities as the claimed compounds. Exemplary derivatives include salts, esters, amides, salts of esters or amides, and N-oxides of a parent compound.

[0048] As used herein, the term "pharmaceutically acceptable carrier" refers to sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants. These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms can be ensured by the inclusion of various antibacterial and antifungal agents such as paraben, chlorobutanol, phenol, sorbic acid and the like. It can also be desirable to include isotonic agents such as sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents, such as aluminum monostearate and gelatin, which delay absorption. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide, poly(orthoesters) and poly(anhydrides). Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues. The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions, which can be dissolved or dispersed in sterile water or other sterile injectable media just prior to use. Suitable inert carriers can include sugars such as lactose. Desirably, at least 95% by weight of the particles of the active ingredient have an effective particle size in the range of 0.01 to 10 micrometers.

[0049] As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, and aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described below. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms, such as nitrogen, can have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This disclosure is not intended to be limited in any manner by the permissible substituents of organic compounds. Also, the terms "substitution" or "substituted with" include the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., a compound that does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. It is also contemplated that, in certain aspects, unless expressly indicated to the contrary, individual substituents can be further optionally substituted (i.e., further substituted or unsubstituted).

[0050] In defining various terms, "A^1," "A^2," "A^3," and "A^4" are used herein as generic symbols to represent various specific substituents. These symbols can be any substituent, not limited to those disclosed herein, and when they are defined to be certain substituents in one instance, they can, in another instance, be defined as some other substituents.

[0051] The term "aliphatic" or "aliphatic group," as used herein, denotes a hydrocarbon moiety that may be straight chain (i.e., unbranched), branched, or cyclic (including fused, bridging, and spirofused polycyclic) and may be completely saturated or may contain one or more units of unsaturation, but which is not aromatic. Unless otherwise specified, aliphatic groups contain 1-20 carbon atoms. Aliphatic groups include, but are not limited to, linear or branched, alkyl, alkenyl, and alkynyl groups, and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0052] The term "alkyl" as used herein is a branched or unbranched saturated hydrocarbon group of 1 to 24 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl, t-butyl, n-pentyl, isopentyl, s-pentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, dodecyl, tetra-

decyl, hexadecyl, eicosyl, tetracosyl, and the like. The alkyl group can be cyclic or acyclic. The alkyl group can be branched or unbranched. The alkyl group can also be substituted or unsubstituted. For example, the alkyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol, as described herein. A "lower alkyl" group is an alkyl group containing from one to six (e.g., from one to four) carbon atoms. The term alkyl group can also be a C1 alkyl, C1-C2 alkyl, C1-C3 alkyl, C1-C4 alkyl, C1-C5 alkyl, C1-C6 alkyl, C1-C7 alkyl, C1-C8 alkyl, C1-C9 alkyl, C1-C10 alkyl, and the like up to and including a C1-C24 alkyl.

[0053] Throughout the specification "alkyl" is generally used to refer to both unsubstituted alkyl groups and substituted alkyl groups; however, substituted alkyl groups are also specifically referred to herein by identifying the specific substituent(s) on the alkyl group. For example, the term "halogenated alkyl" or "haloalkyl" specifically refers to an alkyl group that is substituted with one or more halide, e.g., fluorine, chlorine, bromine, or iodine. Alternatively, the term "monohaloalkyl" specifically refers to an alkyl group that is substituted with a single halide, e.g. fluorine, chlorine, bromine, or iodine. The term "polyhaloalkyl" specifically refers to an alkyl group that is independently substituted with two or more halides, i.e. each halide substituent need not be the same halide as another halide substituent, nor do the multiple instances of a halide substituent need to be on the same carbon. The term "alkoxyalkyl" specifically refers to an alkyl group that is substituted with one or more alkoxy groups, as described below. The term "aminoalkyl" specifically refers to an alkyl group that is substituted with one or more amino groups. The term "hydroxyalkyl" specifically refers to an alkyl group that is substituted with one or more hydroxy groups. When "alkyl" is used in one instance and a specific term such as "hydroxyalkyl" is used in another, it is not meant to imply that the term "alkyl" does not also refer to specific terms such as "hydroxyalkyl" and the like.

[0054] This practice is also used for other groups described herein. That is, while a term such as "cycloalkyl" refers to both unsubstituted and substituted cycloalkyl moieties, the substituted moieties can, in addition, be specifically identified herein; for example, a particular substituted cycloalkyl can be referred to as, e.g., an "alkylcycloalkyl." Similarly, a substituted alkoxy can be specifically referred to as, e.g., a "halogenated alkoxy," a particular substituted alkenyl can be, e.g., an "alkenylalcohol," and the like. Again, the practice of using a general term, such as "cycloalkyl," and a specific term, such as "alkylcycloalkyl," is not meant to imply that the general term does not also include the specific term.

[0055] The term "cycloalkyl" as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like. The term "heterocycloalkyl" is a type of cycloalkyl group as defined above, and is included within the meaning of the term "cycloalkyl," where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkyl group and heterocycloalkyl group can be substituted or unsubstituted. The cycloalkyl group and heterocycloalkyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0056] The term "polyalkylene group" as used herein is a group having two or more CH_2 groups linked to one another. The polyalkylene group can be represented by the formula $-(CH_2)_a-$, where "a" is an integer of from 2 to 500.

[0057] The terms "alkoxy" and "alkoxyl" as used herein to refer to an alkyl or cycloalkyl group bonded through an ether linkage; that is, an "alkoxy" group can be defined as $-OA^1$ where A_1 is alkyl or cycloalkyl as defined above. "Alkoxy" also includes polymers of alkoxy groups as just described; that is, an alkoxy can be a polyether such as $-OA^1-OA^2$ or $-OA^1-(OA^2)_a-OA^3$, where "a" is an integer of from 1 to 200 and A^1, A^2, and A^3 are alkyl and/or cycloalkyl groups.

[0058] The term "alkenyl" as used herein is a hydrocarbon group of from 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon double bond. Asymmetric structures such as $(A^1A^2)C{=}C(A^3A^4)$ are intended to include both the E and Z isomers. This can be presumed in structural formulae herein wherein an asymmetric alkene is present, or it can be explicitly indicated by the bond symbol C=C. The alkenyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

[0059] The term "cycloalkenyl" as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms and containing at least one carbon-carbon double bound, i.e., C=C. Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, norbornenyl, and the like. The term "heterocycloalkenyl" is a type of cycloalkenyl group as defined above, and is included within the meaning of the term "cycloalkenyl," where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkenyl group and heterocycloalkenyl group can be substituted or unsubstituted. The cycloalkenyl group and heterocycloalkenyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0060] The term "alkynyl" as used herein is a hydrocarbon group of 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon triple bond. The alkynyl group can be unsubstituted or substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

[0061] The term "cycloalkynyl" as used herein is a non-aromatic carbon-based ring composed of at least seven carbon atoms and containing at least one carbon-carbon triple bound. Examples of cycloalkynyl groups include, but are not limited to, cycloheptynyl, cyclooctynyl, cyclononynyl, and the like. The term "heterocycloalkynyl" is a type of cycloalkenyl group as defined above, and is included within the meaning of the term "cycloalkynyl," where at least one of the carbon atoms of the ring is replaced with a heteroatom

such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. The cycloalkynyl group and heterocycloalkynyl group can be substituted or unsubstituted. The cycloalkynyl group and heterocycloalkynyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0062] The term "aromatic group" as used herein refers to a ring structure having cyclic clouds of delocalized π electrons above and below the plane of the molecule, where the π clouds contain (4n+2)π electrons. A further discussion of aromaticity is found in Morrison and Boyd, Organic Chemistry, (5th Ed., 1987), Chapter 13, entitled "Aromaticity," pages 477-497, incorporated herein by reference. The term "aromatic group" is inclusive of both aryl and heteroaryl groups.

[0063] The term "aryl" as used herein is a group that contains any carbon-based aromatic group including, but not limited to, benzene, naphthalene, phenyl, biphenyl, anthracene, and the like. The aryl group can be substituted or unsubstituted. The aryl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, —NH_2, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein. The term "biaryl" is a specific type of aryl group and is included in the definition of "aryl." In addition, the aryl group can be a single ring structure or comprise multiple ring structures that are either fused ring structures or attached via one or more bridging groups such as a carbon-carbon bond. For example, biaryl can be two aryl groups that are bound together via a fused ring structure, as in naphthalene, or are attached via one or more carbon-carbon bonds, as in biphenyl.

[0064] The term "aldehyde" as used herein is represented by the formula —C(O)H. Throughout this specification "C(O)" is a short hand notation for a carbonyl group, i.e., C═O.

[0065] The terms "amine" or "amino" as used herein are represented by the formula —NA^1A^2, where A^1 and A^2 can be, independently, hydrogen or alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. A specific example of amino is —NH_2.

[0066] The term "alkylamino" as used herein is represented by the formula —NH(-alkyl) where alkyl is a described herein. Representative examples include, but are not limited to, methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, (sec-butyl)amino group, (tert-butyl) amino group, pentylamino group, isopentylamino group, (tert-pentyl)amino group, hexylamino group, and the like.

[0067] The term "dialkylamino" as used herein is represented by the formula —$N(\text{-alkyl})_2$ where alkyl is a described herein. Representative examples include, but are not limited to, dimethylamino group, diethylamino group, dipropylamino group, diisopropylamino group, dibutylamino group, diisobutylamino group, di(sec-butyl)amino group, di(tert-butyl)amino group, dipentylamino group, diisopentylamino group, di(tert-pentyl)amino group, dihexylamino group, N-ethyl-N-methylamino group, N-methyl-N-propylamino group, N-ethyl-N-propylamino group and the like.

[0068] The term "carboxylic acid" as used herein is represented by the formula —C(O)OH.

[0069] The term "ester" as used herein is represented by the formula —$OC(O)A^1$ or —$C(O)OA^1$, where A^1 can be alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "polyester" as used herein is represented by the formula $-(A^1O(O)C\text{-}A^2\text{-}C(O)O)_a$— or $-(A^1O(O)C\text{-}A^2\text{-}OC(O))_a$—, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and "a" is an integer from 1 to 500. "Polyester" is as the term used to describe a group that is produced by the reaction between a compound having at least two carboxylic acid groups with a compound having at least two hydroxyl groups.

[0070] The term "ether" as used herein is represented by the formula $A^1\text{-}OA^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein. The term "polyether" as used herein is represented by the formula $-(A^1O\text{-}A^2O)_a$—, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and "a" is an integer of from 1 to 500. Examples of polyether groups include polyethylene oxide, polypropylene oxide, and polybutylene oxide.

[0071] The terms "halo," "halogen," or "halide," as used herein can be used interchangeably and refer to F, Cl, Br, or I.

[0072] The terms "pseudohalide," "pseudohalogen," or "pseudohalo," as used herein can be used interchangeably and refer to functional groups that behave substantially similar to halides. Such functional groups include, by way of example, cyano, thiocyanato, azido, trifluoromethyl, trifluoromethoxy, perfluoroalkyl, and perfluoroalkoxy groups.

[0073] The term "heteroalkyl," as used herein refers to an alkyl group containing at least one heteroatom. Suitable heteroatoms include, but are not limited to, O, N, Si, P and S, wherein the nitrogen, phosphorous and sulfur atoms are optionally oxidized, and the nitrogen heteroatom is optionally quaternized. Heteroalkyls can be substituted as defined above for alkyl groups.

[0074] The term "heteroaryl," as used herein refers to an aromatic group that has at least one heteroatom incorporated within the ring of the aromatic group. Examples of heteroatoms include, but are not limited to, nitrogen, oxygen, sulfur, and phosphorus, where N-oxides, sulfur oxides, and dioxides are permissible heteroatom substitutions. The heteroaryl group can be substituted or unsubstituted. The heteroaryl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol as described herein. Heteroaryl groups can be monocyclic, or alternatively fused ring systems. Heteroaryl groups include, but are not limited to, furyl, imidazolyl, pyrimidinyl, tetrazolyl, thienyl, pyridinyl, pyrrolyl, N-methylpyrrolyl, quinolinyl, isoquinolinyl, pyrazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridazinyl, pyrazinyl, benzofuranyl, benzodioxolyl, benzothiophenyl, indolyl, indazolyl, benzimidazolyl, imidazopyridinyl, pyrazolopyridinyl, and pyrazolopyrimidinyl.

Further not limiting examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiophenyl, pyrazolyl, imidazolyl, benzo[d]oxazolyl, benzo[d]thiazolyl, quinolinyl, quinazolinyl, indazolyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrazinyl, benzo[c][1,2,5]thiadiazolyl, benzo[c][1,2,5]oxadiazolyl, and pyrido[2,3-b]pyrazinyl.

[0075] The terms "heterocycle" or "heterocyclyl," as used herein can be used interchangeably and refer to single and multi-cyclic aromatic or non-aromatic ring systems in which at least one of the ring members is other than carbon. Thus, the term is inclusive of, but not limited to, "heterocycloalkyl", "heteroaryl", "bicyclic heterocycle" and "polycyclic heterocycle." Heterocycle includes pyridine, pyrimidine, furan, thiophene, pyrrole, isoxazole, isothiazole, pyrazole, oxazole, thiazole, imidazole, oxazole, including, 1,2,3-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole, thiadiazole, including, 1,2,3-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole, triazole, including, 1,2,3-triazole, 1,3,4-triazole, tetrazole, including 1,2,3,4-tetrazole and 1,2,4,5-tetrazole, pyridazine, pyrazine, triazine, including 1,2,4-triazine and 1,3,5-triazine, tetrazine, including 1,2,4,5-tetrazine, pyrrolidine, piperidine, piperazine, morpholine, azetidine, tetrahydropyran, tetrahydrofuran, dioxane, and the like. The term heterocyclyl group can also be a C2 heterocyclyl, C2-C3 heterocyclyl, C2-C4 heterocyclyl, C2-C5 heterocyclyl, C2-C6 heterocyclyl, C2-C7 heterocyclyl, C2-C8 heterocyclyl, C2-C9 heterocyclyl, C2-C10 heterocyclyl, C2-C11 heterocyclyl, and the like up to and including a C2-C18 heterocyclyl. For example, a C2 heterocyclyl comprises a group which has two carbon atoms and at least one heteroatom, including, but not limited to, aziridinyl, diazetidinyl, dihydrodiazetyl, oxiranyl, thiiranyl, and the like. Alternatively, for example, a C5 heterocyclyl comprises a group which has five carbon atoms and at least one heteroatom, including, but not limited to, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, diazepanyl, pyridinyl, and the like. It is understood that a heterocyclyl group may be bound either through a heteroatom in the ring, where chemically possible, or one of carbons comprising the heterocyclyl ring.

[0076] The term "bicyclic heterocycle" or "bicyclic heterocyclyl," as used herein refers to a ring system in which at least one of the ring members is other than carbon. Bicyclic heterocyclyl encompasses ring systems wherein an aromatic ring is fused with another aromatic ring, or wherein an aromatic ring is fused with a non-aromatic ring. Bicyclic heterocyclyl encompasses ring systems wherein a benzene ring is fused to a 5- or a 6-membered ring containing 1, 2 or 3 ring heteroatoms or wherein a pyridine ring is fused to a 5- or a 6-membered ring containing 1, 2 or 3 ring heteroatoms. Bicyclic heterocyclic groups include, but are not limited to, indolyl, indazolyl, pyrazolo[1,5-a]pyridinyl, benzofuranyl, quinolinyl, quinoxalinyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, 3,4-dihydro-2H-chromenyl, 1H-pyrazolo[4,3-c]pyridin-3-yl; 1H-pyrrolo[3,2-b]pyridin-3-yl; and 1H-pyrazolo[3,2-b]pyridin-3-yl.

[0077] The term "heterocycloalkyl" as used herein refers to an aliphatic, partially unsaturated or fully saturated, 3- to 14-membered ring system, including single rings of 3 to 8 atoms and bi- and tricyclic ring systems. The heterocycloalkyl ring-systems include one to four heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein a nitrogen and sulfur heteroatom optionally can be oxidized and a nitrogen heteroatom optionally can be substituted. Representative heterocycloalkyl groups include, but are not limited to, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl.

[0078] The term "hydroxyl" or "hydroxyl" as used herein is represented by the formula —OH.

[0079] The term "ketone" as used herein is represented by the formula $A^1C(O)A^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0080] The term "azide" or "azido" as used herein is represented by the formula $—N_3$.

[0081] The term "nitro" as used herein is represented by the formula $—NO_2$.

[0082] The term "nitrile" or "cyano" as used herein is represented by the formula —CN.

[0083] The term "silyl" as used herein is represented by the formula $—SiA^1A^2A^3$, where A^1, A^2, and A^3 can be, independently, hydrogen or an alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0084] The term "sulfo-oxo" as used herein is represented by the formulas $—S(O)A^1$, $—S(O)_2A^1$, $—OS(O)_2A^1$, or $—OS(O)_2OA^1$, where A^1 can be hydrogen or an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. Throughout this specification "S(O)" is a short hand notation for S═O. The term "sulfonyl" is used herein to refer to the sulfo-oxo group represented by the formula $—S(O)_2A^1$, where A^1 can be hydrogen or an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "sulfone" as used herein is represented by the formula $A^1S(O)_2A^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "sulfoxide" as used herein is represented by the formula $A^1S(O)A^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0085] The term "thiol" as used herein is represented by the formula SH.

[0086] "R^1," "R^2," "R^3," "R^n," where n is an integer, as used herein can, independently, possess one or more of the groups listed above. For example, if R^1 is a straight chain alkyl group, one of the hydrogen atoms of the alkyl group can optionally be substituted with a hydroxyl group, an alkoxy group, an alkyl group, a halide, and the like. Depending upon the groups that are selected, a first group can be incorporated within second group or, alternatively, the first group can be pendant (i.e., attached) to the second group. For example, with the phrase "an alkyl group comprising an amino group," the amino group can be incorporated within the backbone of the alkyl group. Alternatively, the amino group can be attached to the backbone of the alkyl group. The nature of the group(s) that is (are) selected will determine if the first group is embedded or attached to the second group.

[0087] As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogen of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted"

group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. In is also contemplated that, in certain aspects, unless expressly indicated to the contrary, individual substituents can be further optionally substituted (i.e., further substituted or unsubstituted).

[0088] The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain aspects, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0089] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; $—(CH_2)_{0-4}R^\circ$; $—(CH_2)_{0-4}OR^\circ$; $—O(CH_2)_{0-4}R^\circ$, $—O—(CH_2)_{0-4}C(O)OR^\circ$; $—(CH_2)_{0-4}CH(OR^\circ)_2$; $—(CH_2)_{0-4}SR^\circ$; $—(CH_2)_{0-4}$ Ph, which may be substituted with R°; $—(CH_2)_{0-4}O(CH_2)_{0-1}$-Ph which may be substituted with R°; —CH═CHPh, which may be substituted with R°; $—(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $—NO_2$; —CN; $—N_3$; $—(CH_2)_{0-4}N(R^\circ)_2$; $—(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $N(R^\circ)C(S)R^\circ$; $—(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $—N(R^\circ)C(S)NR^\circ_2$; $—(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $—N(R^\circ)N(R^\circ)C(O)R^\circ$; $—N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $—N(R^\circ)N(R^\circ)C(O)OR^\circ$; $—(CH_2)_{0-4}C(O)R^\circ$; $—C(S)R^\circ$; $—(CH_2)_{0-4}C(O)OR^\circ$; $—(CH_2)_{0-4}C(O)SR^\circ$; $—(CH_2)_{0-4}C(O)OSiR^\circ_3$; $—(CH_2)_{0-4}OC(O)R^\circ$; $—OC(O)(CH_2)_{0-4}SR—$, SC(S)SR°; $—(CH_2)_{0-4}SC(O)R^\circ$; $—(CH_2)_{0-4}C(O)NR^\circ_2$; $—C(S)NR^\circ_2$; $—C(S)SR^\circ$; $—(CH_2)_{0-4}OC(O)NR^\circ_2$; $—C(O)N(OR^\circ)R^\circ$; $—C(O)C(O)R^\circ$; $—C(O)CH_2C(O)R^\circ$; $—C(NOR^\circ)R^\circ$; $—(CH_2)_{0-4}SSR^\circ$; $—(CH_2)_{0-4}S(O)_2R^\circ$; $—(CH_2)_{0-4}S(O)_2OR^\circ$; $—(CH_2)_{0-4}OS(O)_2R^\circ$; $S(O)_2NR^\circ_2$; $—(CH_2)_{0-4}S(O)R^\circ$; $—N(R^\circ)S(O)_2NR^\circ_2$; $—N(R^\circ)S(O)_2R^\circ$; $—N(OR^\circ)R^\circ$; $—C(NH)NR^\circ_2$; $—P(O)_2R^\circ$; $—P(O)R^\circ_2$; $—OP(O)R^\circ_2$; $—OP(O)(OR^\circ)_2$; SiR°_3; $—(C_{1-4}$ straight or branched)alkylene)O—$N(R^\circ)_2$; or $—(C_{1-4}$ straight or branched)alkylene)C(O)O—$N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $—CH_2Ph$, $—O(CH_2)_{0-1}Ph$, $—CH_2$-(5-6-membered heteroaryl ring), or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0090] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $—(CH_2)_{0-2}R^\bullet$, -(haloR•), $—(CH_2)_{0-2}OH$, $—(CH_2)_{0-2}OR^\bullet$, $—(CH_2)_{0-2}CH(OR^\bullet)_2$; —O(haloR•), —CN, $—N_3$, $—(CH_2)_{0-2}C(O)R^\bullet$, $—(CH_2)_{0-2}C(O)OH$, $—(CH_2)_{0-2}C(O)OR^\bullet$, $—(CH_2)_{0-2}SR^\bullet$, $—(CH_2)_{0-2}SH$, $—(CH_2)_{0-2}NH_2$, $—(CH_2)_{0-2}NHR^\bullet$, $—(CH_2)_{0-2}NR^\bullet_2$, $—NO_2$, $—SiR^\bullet_3$, $—OSiR^\bullet_3$, $—C(O)SR^\bullet$, $—(C_{1-4}$ straight or branched alkylene)C(O)$OR^\bullet$, or $—SSR^\bullet$ wherein each R• is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $—CH_2Ph$, $—O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include ═O and ═S.

[0091] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: ═O, ═S, $═NNR^*_2$, ═NNHC(O)R*, ═NNHC(O)OR*, $═NNHS(O)_2R^*$, ═NR*, ═NOR*, $—O(C(R^*_2))_{2-3}O—$, or $—S(C(R^*_2))_{2-3}S—$, wherein each independent occurrence of R* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $—O(CR^*_2)_{2-3}O—$, wherein each independent occurrence of R* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0092] Suitable substituents on the aliphatic group of R* include halogen, $—R^\bullet$, -(haloR•), —OH, $—OR^\bullet$, —O(haloR•), —CN, —C(O)OH, $—C(O)OR^\bullet$, $—NH_2$, $—NHR^\bullet$, $—NR^\bullet_2$, or $—NO_2$, wherein each R• is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $—CH_2Ph$, $—O(CH_2)_{0-1}Ph$, or a 5-6 membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0093] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $—R^\dagger$, $—NR^\dagger_2$, $—C(O)R^\dagger$, $—C(O)OR^\dagger$, $—C(O)C(O)R^\dagger$, $—C(O)CH_2C(O)R^\dagger$, $—S(O)_2R^\dagger$, $—S(O)_2NR^\dagger_2$, $—C(S)NR^\dagger_2$, $—C(NH)NR^\dagger_2$, or $—N(R^\dagger)S(O)_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted —OPh, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3-12-membered saturated, partially unsaturated, or aryl mono or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0094] Suitable substituents on the aliphatic group of $R^\dagger$ are independently halogen, $—R^\bullet$, -(haloR•), —OH, $—OR^\bullet$, —O(haloR•), —CN, —C(O)OH, $—C(O)OR^\bullet$, $—NH_2$, $—NHR^\bullet$, $—NR^\bullet_2$, or $—NO_2$, wherein each R• is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $—CH_2Ph$, $—O(CH_2)_{0-1}Ph$, or a 5-6 membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

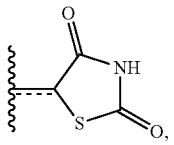
[0095] The term "leaving group" refers to an atom (or a group of atoms) with electron withdrawing ability that can be displaced as a stable species, taking with it the bonding electrons. Examples of suitable leaving groups include halides and sulfonate esters, including, but not limited to, triflate, mesylate, tosylate, and brosylate.

[0096] The terms "hydrolysable group" and "hydrolysable moiety" refer to a functional group capable of undergoing

hydrolysis, e.g., under basic or acidic conditions. Examples of hydrolysable residues include, without limitation, acid halides, activated carboxylic acids, and various protecting groups known in the art (see, for example, "Protective Groups in Organic Synthesis," T. W. Greene, P. G. M. Wuts, Wiley-Interscience, 1999).

[0097] The term "organic residue" defines a carbon-containing residue, i.e., a residue comprising at least one carbon atom, and includes but is not limited to the carbon-containing groups, residues, or radicals defined hereinabove. Organic residues can contain various heteroatoms, or be bonded to another molecule through a heteroatom, including oxygen, nitrogen, sulfur, phosphorus, or the like. Examples of organic residues include but are not limited alkyl or substituted alkyls, alkoxy or substituted alkoxy, mono or di-substituted amino, amide groups, etc. Organic residues can preferably comprise 1 to 18 carbon atoms, 1 to 15, carbon atoms, 1 to 12 carbon atoms, 1 to 8 carbon atoms, 1 to 6 carbon atoms, or 1 to 4 carbon atoms. In a further aspect, an organic residue can comprise 2 to 18 carbon atoms, 2 to 15, carbon atoms, 2 to 12 carbon atoms, 2 to 8 carbon atoms, 2 to 4 carbon atoms, or 2 to 4 carbon atoms.

[0098] A very close synonym of the term "residue" is the term "radical," which as used in the specification and concluding claims, refers to a fragment, group, or substructure of a molecule described herein, regardless of how the molecule is prepared. For example, a 2,4-thiazolidinedione radical in a particular compound has the structure:



regardless of whether thiazolidinedione is used to prepare the compound. In some embodiments the radical (for example an alkyl) can be further modified (i.e., substituted alkyl) by having bonded thereto one or more "substituent radicals." The number of atoms in a given radical is not critical to the present invention unless it is indicated to the contrary elsewhere herein.

[0099] "Organic radicals," as the term is defined and used herein, contain one or more carbon atoms. An organic radical can have, for example, 1-26 carbon atoms, 1-18 carbon atoms, 1-12 carbon atoms, 1-8 carbon atoms, 1-6 carbon atoms, or 1-4 carbon atoms. In a further aspect, an organic radical can have 2-26 carbon atoms, 2-18 carbon atoms, 2-12 carbon atoms, 2-8 carbon atoms, 2-6 carbon atoms, or 2-4 carbon atoms. Organic radicals often have hydrogen bound to at least some of the carbon atoms of the organic radical. One example, of an organic radical that comprises no inorganic atoms is a 5, 6, 7, 8-tetrahydro-2-naphthyl radical. In some embodiments, an organic radical can contain 1-10 inorganic heteroatoms bound thereto or therein, including halogens, oxygen, sulfur, nitrogen, phosphorus, and the like. Examples of organic radicals include but are not limited to an alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, mono-substituted amino, di-substituted amino, acyloxy, cyano, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, alkylsulfonyl, alkylsulfonyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy, haloalkyl, haloalkoxy, aryl, substituted aryl, heteroaryl, heterocyclic, or substituted heterocyclic radicals, wherein the terms are defined elsewhere herein. A few non-limiting examples of organic radicals that include heteroatoms include alkoxy radicals, trifluoromethoxy radicals, acetoxy radicals, dimethylamino radicals and the like.

[0100] Compounds described herein can contain one or more double bonds and, thus, potentially give rise to cis/trans (E/Z) isomers, as well as other conformational isomers. Unless stated to the contrary, the invention includes all such possible isomers, as well as mixtures of such isomers.

[0101] Unless stated to the contrary, a formula with chemical bonds shown only as solid lines and not as wedges or dashed lines contemplates each possible isomer, e.g., each enantiomer and diastereomer, and a mixture of isomers, such as a racemic or scalemic mixture. Compounds described herein can contain one or more asymmetric centers and, thus, potentially give rise to diastereomers and optical isomers. Unless stated to the contrary, the present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. Mixtures of stereoisomers, as well as isolated specific stereoisomers, are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

[0102] Many organic compounds exist in optically active forms having the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (−) are employed to designate the sign of rotation of plane-polarized light by the compound, with (−) or meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that they are non-superimposable mirror images of one another. A specific stereoisomer can also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture. Many of the compounds described herein can have one or more chiral centers and therefore can exist in different enantiomeric forms. If desired, a chiral carbon can be designated with an asterisk (*). When bonds to the chiral carbon are depicted as straight lines in the disclosed formulas, it is understood that both the (R) and (S) configurations of the chiral carbon, and hence both enantiomers and mixtures thereof, are embraced within the formula. As is used in the art, when it is desired to specify the absolute configuration about a chiral carbon, one of the bonds to the chiral carbon can be depicted as a wedge (bonds to atoms above the plane) and the other can be depicted as a series or wedge of short parallel lines is (bonds to atoms below the plane). The Cahn-Ingold-Prelog system can be used to assign the (R) or (S) configuration to a chiral carbon.

[0103] When the disclosed compounds contain one chiral center, the compounds exist in two enantiomeric forms. Unless specifically stated to the contrary, a disclosed compound includes both enantiomers and mixtures of enantiom-

ers, such as the specific 50:50 mixture referred to as a racemic mixture. The enantiomers can be resolved by methods known to those skilled in the art, such as formation of diastereoisomeric salts which may be separated, for example, by crystallization (see, CRC Handbook of Optical Resolutions via Diastereomeric Salt Formation by David Kozma (CRC Press, 2001)); formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step can liberate the desired enantiomeric form. Alternatively, specific enantiomers can be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

[0104] Designation of a specific absolute configuration at a chiral carbon in a disclosed compound is understood to mean that the designated enantiomeric form of the compounds can be provided in enantiomeric excess (e.e.). Enantiomeric excess, as used herein, is the presence of a particular enantiomer at greater than 50%, for example, greater than 60%, greater than 70%, greater than 75%, greater than 80%, greater than 85%, greater than 90%, greater than 95%, greater than 98%, or greater than 99%. In one aspect, the designated enantiomer is substantially free from the other enantiomer. For example, the "R" forms of the compounds can be substantially free from the "S" forms of the compounds and are, thus, in enantiomeric excess of the "S" forms. Conversely, "S" forms of the compounds can be substantially free of "R" forms of the compounds and are, thus, in enantiomeric excess of the "R" forms.

[0105] When a disclosed compound has two or more chiral carbons, it can have more than two optical isomers and can exist in diastereoisomeric forms. For example, when there are two chiral carbons, the compound can have up to four optical isomers and two pairs of enantiomers ((S,S)/(R,R) and (R,S)/(S,R)). The pairs of enantiomers (e.g., (S,S)/(R,R)) are mirror image stereoisomers of one another. The stereoisomers that are not mirror-images (e.g., (S,S) and (R,S)) are diastereomers. The diastereoisomeric pairs can be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. Unless otherwise specifically excluded, a disclosed compound includes each diastereoisomer of such compounds and mixtures thereof.

[0106] The compounds according to this disclosure may form prodrugs at hydroxyl or amino functionalities using alkoxy, amino acids, etc., groups as the prodrug forming moieties. For instance, the hydroxymethyl position may form mono-, di- or triphosphates and again these phosphates can form prodrugs. Preparations of such prodrug derivatives are discussed in various literature sources (examples are: Alexander et al., J. Med. Chem. 1988, 31, 318; Aligas-Martin et al., PCT WO 2000/041531, p. 30). The nitrogen function converted in preparing these derivatives is one (or more) of the nitrogen atoms of a compound of the disclosure.

[0107] "Derivatives" of the compounds disclosed herein are pharmaceutically acceptable salts, prodrugs, deuterated forms, radioactively labeled forms, isomers, solvates, and combinations thereof. The "combinations" mentioned in this context are refer to derivatives falling within at least two of the groups: pharmaceutically acceptable salts, prodrugs, deuterated forms, radioactively labeled forms, isomers, and solvates. Examples of radioactively labeled forms include compounds labeled with tritium, phosphorous-32, iodine-129, carbon-11, fluorine-18, and the like.

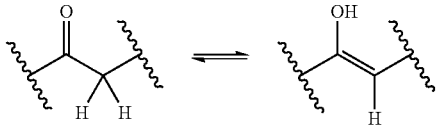
[0108] Compounds described herein comprise atoms in both their natural isotopic abundance and in non-natural abundance. The disclosed compounds can be isotopically labeled or isotopically substituted compounds identical to those described, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F and ^{36}Cl, respectively. Compounds further comprise prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of the present invention and prodrugs thereof can generally be prepared by carrying out the procedures below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

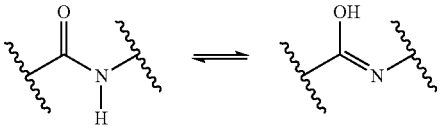
[0109] The compounds described in the invention can be present as a solvate. In some cases, the solvent used to prepare the solvate is an aqueous solution, and the solvate is then often referred to as a hydrate. The compounds can be present as a hydrate, which can be obtained, for example, by crystallization from a solvent or from aqueous solution. In this connection, one, two, three or any arbitrary number of solvent or water molecules can combine with the compounds according to the invention to form solvates and hydrates. Unless stated to the contrary, the invention includes all such possible solvates.

[0110] The term "co-crystal" means a physical association of two or more molecules that owe their stability through non-covalent interaction. One or more components of this molecular complex provide a stable framework in the crystalline lattice. In certain instances, the guest molecules are incorporated in the crystalline lattice as anhydrates or solvates, see e.g. "Crystal Engineering of the Composition of Pharmaceutical Phases. Do Pharmaceutical Co-crystals Represent a New Path to Improved Medicines?" Almaras-

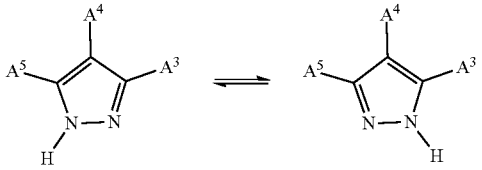
son, O., et. al., The Royal Society of Chemistry, 1889-1896, 2004. Examples of co-crystals include p-toluenesulfonic acid and benzenesulfonic acid.

[0111] It is also appreciated that certain compounds described herein can be present as an equilibrium of tautomers. For example, ketones with an α-hydrogen can exist in an equilibrium of the keto form and the enol form.





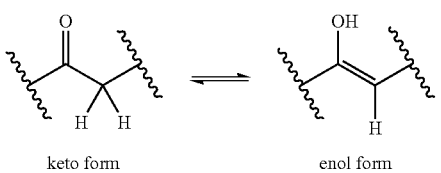
[0112] Likewise, amides with an N-hydrogen can exist in an equilibrium of the amide form and the imidic acid form. As another example, pyrazoles can exist in two tautomeric forms, N^1-unsubstituted, 3-A^3 and N^1-unsubstituted, 5-A^3 as shown below.



Unless stated to the contrary, the invention includes all such possible tautomers.

[0113] It is known that chemical substances form solids that are present in different states of order, which are termed polymorphic forms or modifications. The different modifications of a polymorphic substance can differ greatly in their physical properties. The compounds according to the invention can be present in different polymorphic forms, with it being possible for particular modifications to be metastable. Unless stated to the contrary, the invention includes all such possible polymorphic forms.

[0114] In some aspects, a structure of a compound can be represented by a formula:



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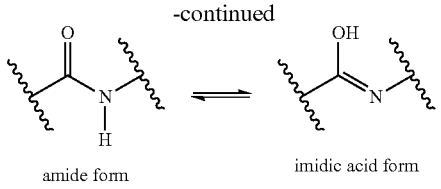
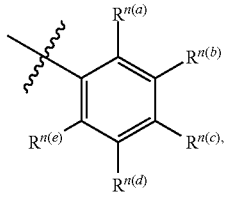


which is understood to be equivalent to a formula:



wherein n is typically an integer. That is, R^n is understood to represent five independent substituents, $R^{n(a)}$, $R^{n(b)}$, $R^{n(c)}$, $R^{n(d)}$, $R^{n(e)}$. By "independent substituents," it is meant that each R substituent can be independently defined. For example, if in one instance $R^{n(a)}$ is halogen, then $R^{n(b)}$ is not necessarily halogen in that instance.

[0115] Certain materials, compounds, compositions, and components disclosed herein can be obtained commercially or readily synthesized using techniques generally known to those of skill in the art. For example, the starting materials and reagents used in preparing the disclosed compounds and compositions are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Acros Organics (Morris Plains, N.J.), Strem Chemicals (Newburyport, Mass.), Fisher Scientific (Pittsburgh, Pa.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and supplemental volumes (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991); March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition); and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

[0116] Unless otherwise expressly stated, it is in no way intended that any method set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not actually recite an order to be followed by its steps or it is not otherwise specifically stated in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including: matters of logic with respect to arrangement of steps or operational flow; plain meaning derived from grammatical organization or punctuation; and the number or type of embodiments described in the specification.

[0117] Disclosed are the components to be used to prepare the compositions of the invention as well as the compositions themselves to be used within the methods disclosed herein. These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while

specific reference of each various individual and collective combinations and permutation of these compounds cannot be explicitly disclosed, each is specifically contemplated and described herein. For example, if a particular compound is disclosed and discussed and a number of modifications that can be made to a number of molecules including the compounds are discussed, specifically contemplated is each and every combination and permutation of the compound and the modifications that are possible unless specifically indicated to the contrary. Thus, if a class of molecules A, B, and C are disclosed as well as a class of molecules D, E, and F and an example of a combination molecule, A-D is disclosed, then even if each is not individually recited each is individually and collectively contemplated meaning combinations, A-E, A-F, B-D, B-E, B-F, C-D, C-E, and C-F are considered disclosed. Likewise, any subset or combination of these is also disclosed. Thus, for example, the sub-group of A-E, B-F, and C-E would be considered disclosed. This concept applies to all aspects of this application including, but not limited to, steps in methods of making and using the compositions of the invention. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific embodiment or combination of embodiments of the methods of the invention.

[0118] It is understood that the compounds and compositions disclosed herein have certain functions. Disclosed herein are certain structural requirements for performing the disclosed functions, and it is understood that there are a variety of structures that can perform the same function that are related to the disclosed structures, and that these structures will typically achieve the same result.

B. Compounds

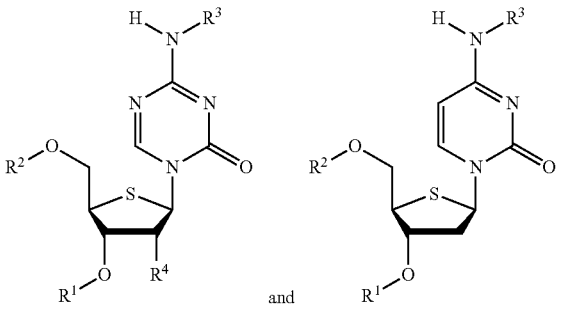
[0119] In one aspect, the invention relates to compounds useful in treating disorders associated with a disorder of uncontrolled cellular proliferation such as, for example, cancers including, but not limited to, sarcomas, carcinomas, hematological cancers, solid tumors, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanomas, gliomas, leukemias, lymphomas, chronic myeloproliferative disorders, myelodysplastic syndromes, myeloproliferative neoplasms, and plasma cell neoplasms (myelomas).

[0120] In one aspect, the compounds of the invention are useful in the treatment of disorders of uncontrolled cellular proliferation, as further described herein.

[0121] It is contemplated that each disclosed derivative can be optionally further substituted. It is also contemplated that any one or more derivative can be optionally omitted from the invention. It is understood that a disclosed compound can be provided by the disclosed methods. It is also understood that the disclosed compounds can be employed in the disclosed methods of using.

[0122] 1. Structure

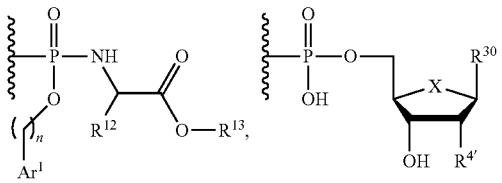
[0123] In one aspect, disclosed are compounds having a structure represented by a formula selected from:



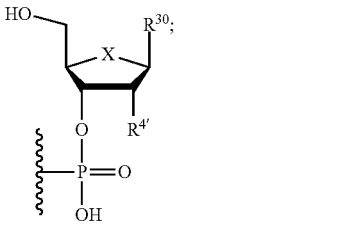
and

,

wherein each of R^1 and R^2 is independently selected from hydrogen, —C(O)R^{10}, —P(O)(OR^{11})$_2$, —P(O)(OH)OP(O)(OH)OP(O)(OH)$_2$, and a structure represented by a formula selected from:

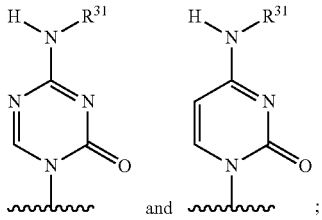


, and

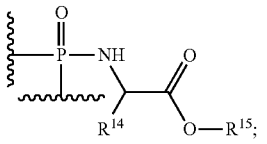


provided that one of R^1 and R^2 is hydrogen; wherein n is selected from 0, 1, and 2; wherein X, when present, is selected from O and S; wherein R^{10}, when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and —CH(NH_2)R^{20}; wherein R^{20}, when present, is selected from hydrogen, methyl, isopropyl, isobutyl, sec-butyl, —$(CH_2)_3NHC(NH)NH_2$, —$(CH_2)_4NH_2$, —CH_2CO_2H, —$(CH_2)_2CO_2H$, —CH_2OH, —$CH(OH)CH_3$, —$CH_2C(O)NH_2$, —$(CH_2)_2C(O)NH_2$, —CH_2SH, —$(CH_2)_2SCH_3$, —CH_2SeH, —$CH_2C_6H_5$, and —CH_2Cy^1; wherein Cy^1, when present, is selected from monocylic aryl, para-hydroxy monocyclic aryl, 4-imidazolyl, and 3-indolyl; wherein each occurrence of RH, when present, is independently selected from hydrogen, —(C1-C10 alkyl)CO_2(C1-C10 alkyl), —(C1-C10 alkoxy)CO_2(C1-C10 alkyl), —(C1-C10 alkyl)CO_2(C1-C10 alkylthio), —(C1-C10 alkyl)-S—S—(C1-C10 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH; wherein Ar^2, when present, is selected from aryl and heteroaryl substituted with 1 or 2 groups independently selected from C1-C10 alkyl and nitro; wherein R^{12}, when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylamino, —(C1-C8)C(O)NH_2, aryl, and —(CH_2)aryl; wherein R^{13}, when present, is

selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar^3; wherein Ar^3, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino; wherein Ar^1, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino; wherein R^{30}, when present, is a structure selected from:

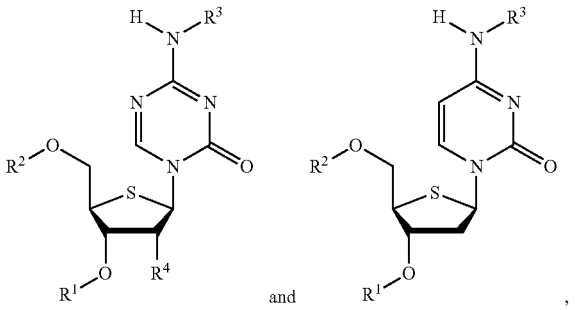


wherein R^{31}, when present, is selected from hydrogen, —C(O)(C1-C30 alkyl), and —C(O)(C2-C30 alkenyl); or wherein each of R^1 and R^2 together comprise a structure represented by a formula:

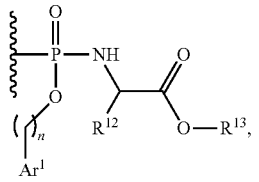


wherein R^{14}, when present, is C1-C8 alkyl; wherein R^{15}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and aryl substituted with 0 or 1 C1-C10 alkyl groups; wherein R^3 is selected from hydrogen, —C(O)(C1-C30 alkyl), and —C(O)(C2-C30 alkenyl); wherein each of R^4 and $R^{4'}$, when present, is independently selected from hydrogen, fluoro, —CN, C2-C4 alkenyl, C2-C4 alkynyl, C1-C4 haloalkyl, and —OR^{16}; and wherein R^{16}, when present, is selected from hydrogen, methyl, and —$C(O)R^{10}$, provided that R^1, R^2, and R^3 are not simultaneously hydrogen, or a pharmaceutically acceptable salt thereof.

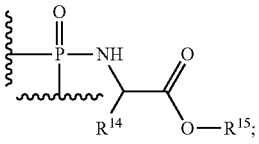
[0124] In one aspect, disclosed are compounds having a structure represented by a formula selected from:



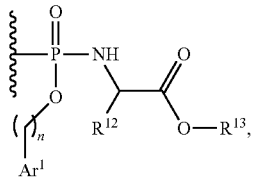
wherein each of R^1 and R^2 is independently selected from hydrogen, —$C(O)R^{10}$, —$P(O)(OR^{11})_2$, and a structure represented by a formula:



provided that one of R^1 and R^2 is hydrogen; wherein n is selected from 0, 1, and 2; wherein R^{10}, when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and —$CH(NH_2)R^{20}$; wherein R^{20}, when present, is selected from hydrogen, methyl, isopropyl, isobutyl, sec-butyl, —$(CH_2)_3NHC(NH)NH_2$, —$(CH_2)_4NH_2$, —CH_2CO_2H, —$(CH_2)_2CO_2H$, —CH_2OH, —$CH(OH)CH_3$, —$CH_2C(O)NH_2$, —$(CH_2)_2C(O)NH_2$, —CH_2SH, —$(CH_2)_2SCH_3$, —CH_2SeH, —$CH_2C_6H_5$, and —CH_2Cy^1; wherein Cy^1, when present, is selected from monocylic aryl, para-hydroxy monocyclic aryl, 4-imidazolyl, and 3-indolyl; wherein each occurrence of RH, when present, is independently selected from hydrogen, —(C1-C10 alkyl)CO_2(C1-C10 alkyl), —(C1-C10 alkoxy)CO_2(C1-C10 alkyl), —(C1-C10 alkyl)CO_2(C1-C10 alkylthio), —(C1-C10 alkyl)-S—S—(C1-C10 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and OH; wherein Ar^2, when present, is selected from aryl and heteroaryl substituted with 1 or 2 groups independently selected from C1-C10 alkyl and nitro; wherein R^{12}, when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylamino, —(C1-C8)$C(O)NH_2$, aryl, and —(CH_2)aryl; wherein R^{13}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and aryl substituted with 0 or 1 C1-C10 alkyl group; wherein Ar^1, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino; or wherein each of R^1 and R^2 together comprise a structure represented by a formula:

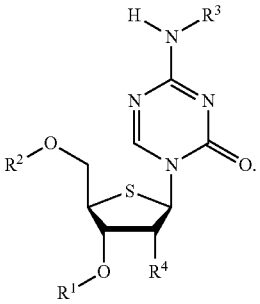


wherein R^{14}, when present, is C1-C8 alkyl; wherein R^{15}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and aryl substituted with 0 or 1 C1-C10 alkyl groups; wherein R^3 is selected from hydrogen, fluoro, —C(O)(C1-C30 alkyl), and —C(O)(C2-C30 alkenyl); wherein R^4, when present, is selected from hydrogen, fluoro, and —OR^{16}; and wherein R^{16}, when present, is selected from hydrogen, methyl, —$C(O)R^{10}$, —$P(O)(OR^{11})_2$, and a structure represented by a formula:

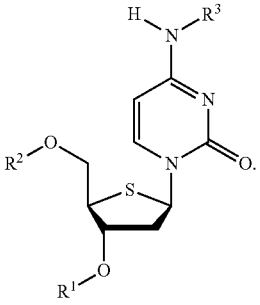


provided that R^1, R^2, and R^3 are not simultaneously hydrogen, or a pharmaceutically acceptable salt thereof.

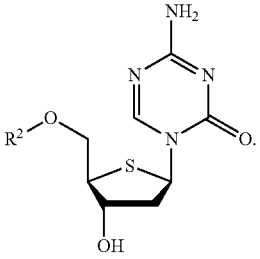
[0125] In a further aspect, the compound has a structure represented by a formula:



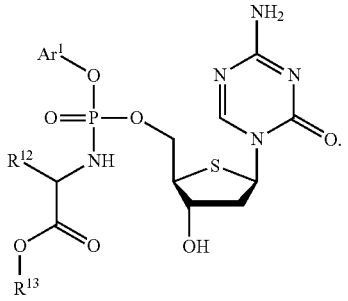
[0126] In a further aspect, the compound has a structure represented by a formula:



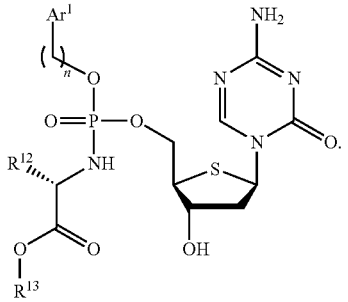
[0127] In a further aspect, the compound has a structure represented by a formula:



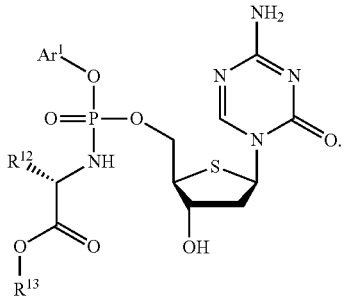
[0128] In a further aspect, the compound has a structure represented by a formula:



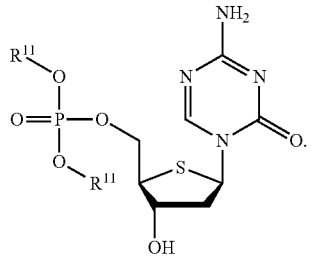
[0129] In a further aspect, the compound has a structure represented by a formula:



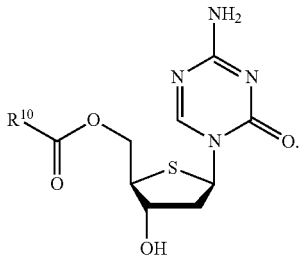
[0130] In a further aspect, the compound has a structure represented by a formula:



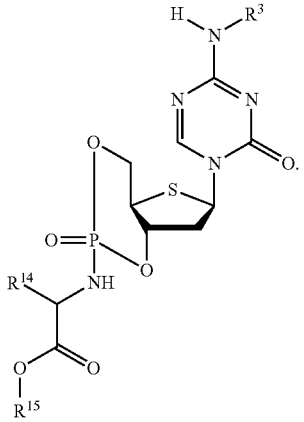
[0131] In a further aspect, the compound has a structure represented by a formula:



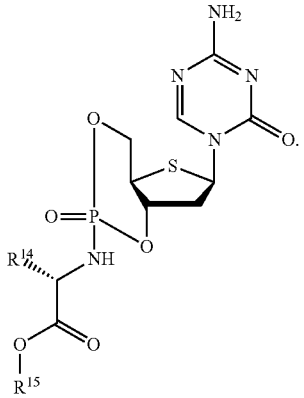
[0132] In a further aspect, the compound has a structure represented by a formula:



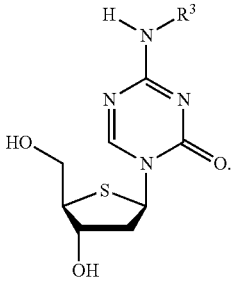
[0133] In a further aspect, the compound has a structure represented by a formula:



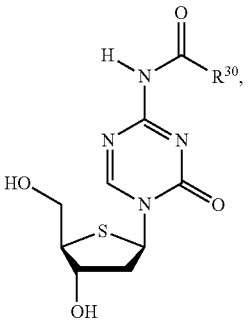
[0134] In a further aspect, the compound has a structure represented by a formula:



[0135] In a further aspect, the compound has a structure represented by a formula:

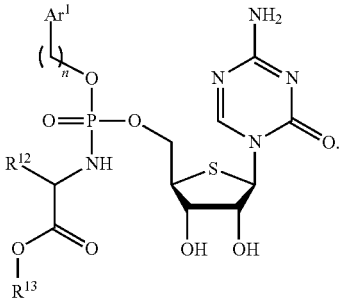


[0136] In a further aspect, the compound has a structure represented by a formula:

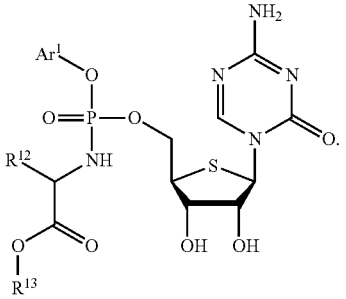


wherein R^{30} is C1-C30 alkyl.

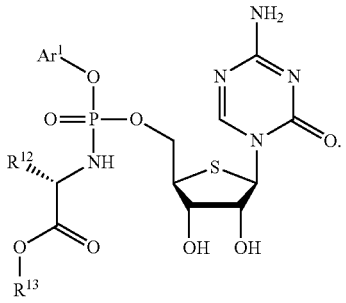
[0137] In a further aspect, the compound has a structure represented by a formula:



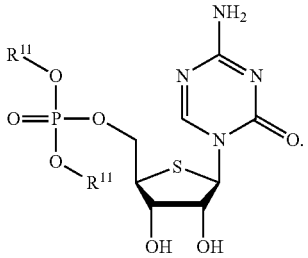
[0138] In a further aspect, the compound has a structure represented by a formula:



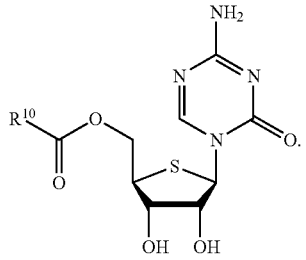
[0139] In a further aspect, the compound has a structure represented by a formula:



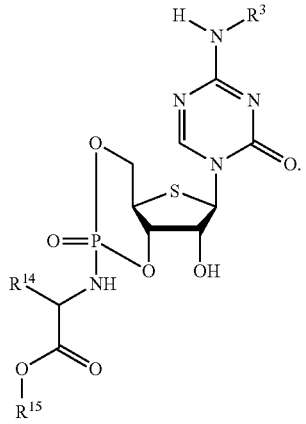
[0140] In a further aspect, the compound has a structure represented by a formula:



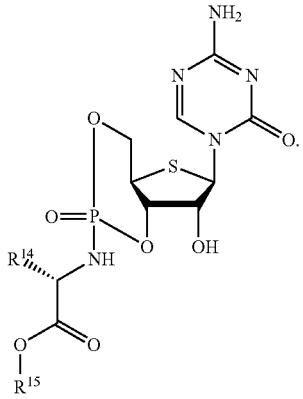
[0141] In a further aspect, the compound has a structure represented by a formula:



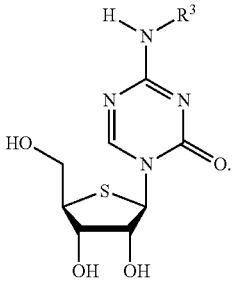
[0142] In a further aspect, the compound has a structure represented by a formula:



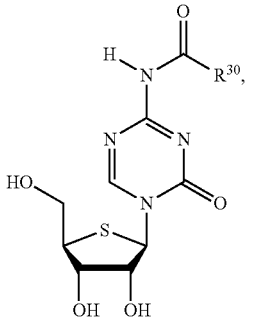
[0143] In a further aspect, the compound has a structure represented by a formula:



[0144] In a further aspect, the compound has a structure represented by a formula:

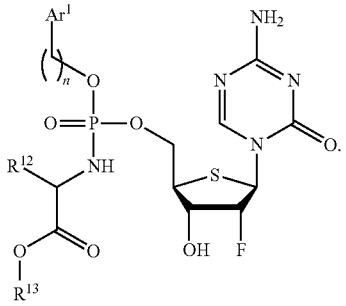


[0145] In a further aspect, the compound has a structure represented by a formula:

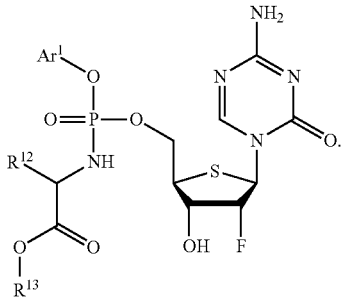


wherein R^{30} is C1-C30 alkyl.

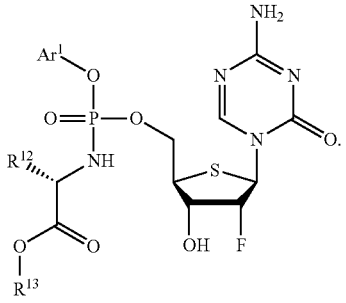
[0146] In a further aspect, the compound has a structure represented by a formula:



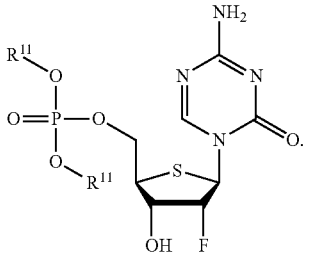
[0147] In a further aspect, the compound has a structure represented by a formula:



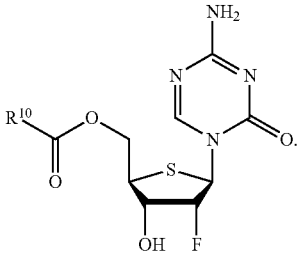
[0148] In a further aspect, the compound has a structure represented by a formula:



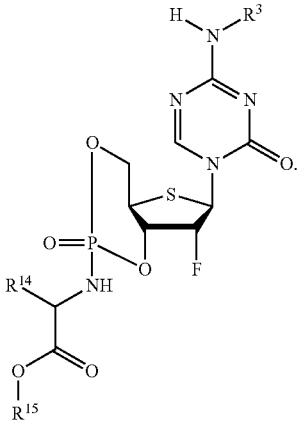
[0149] In a further aspect, the compound has a structure represented by a formula:



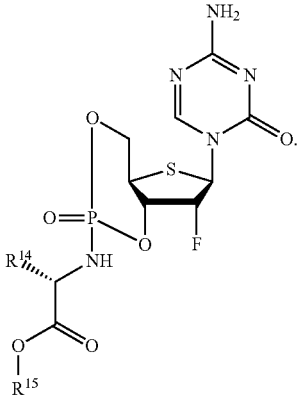
[0150] In a further aspect, the compound has a structure represented by a formula:



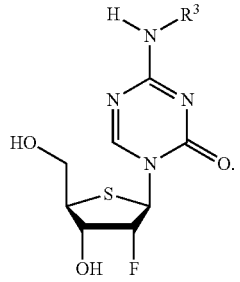
[0151] In a further aspect, the compound has a structure represented by a formula:



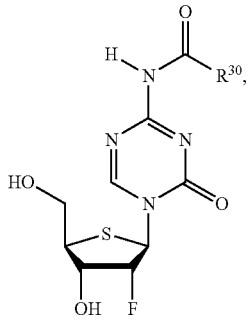
[0152] In a further aspect, the compound has a structure represented by a formula:



[0153] In a further aspect, the compound has a structure represented by a formula:

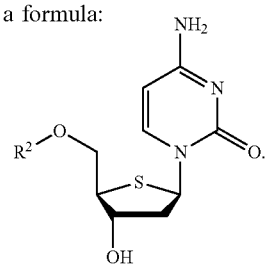


[0154] In a further aspect, the compound has a structure represented by a formula:

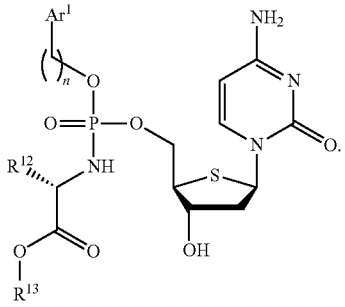


wherein R^{30} is C1-C30 alkyl.

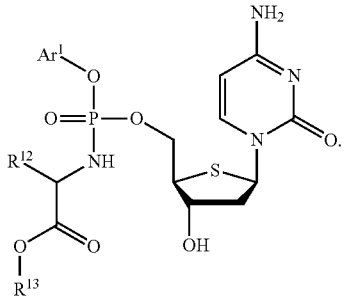
[0155] In a further aspect, the compound has a structure represented by a formula:



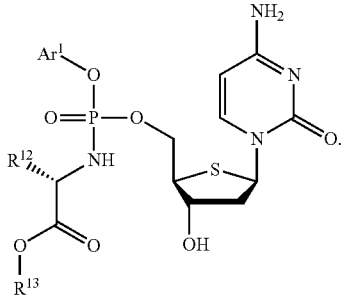
[0156] In a further aspect, the compound has a structure represented by a formula:



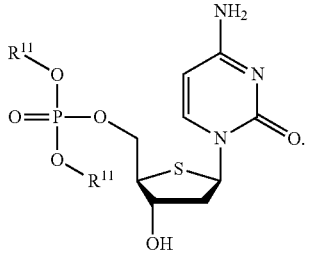
[0157] In a further aspect, the compound has a structure represented by a formula:



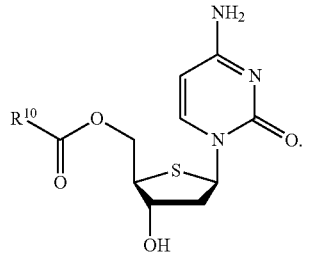
[0158] In a further aspect, the compound has a structure represented by a formula:



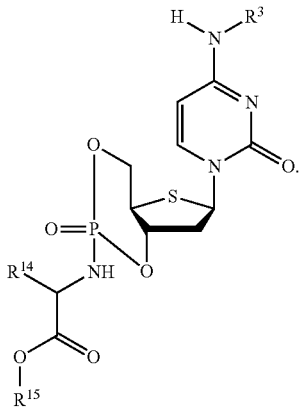
[0159] In a further aspect, the compound has a structure represented by a formula:



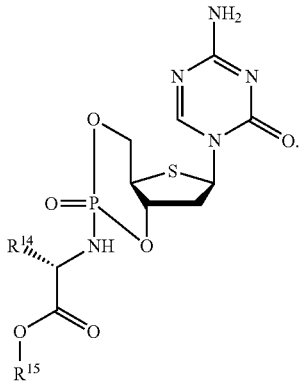
[0160] In a further aspect, the compound has a structure represented by a formula:



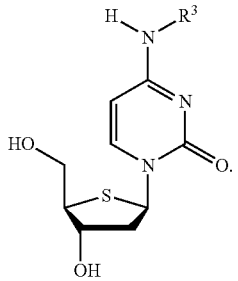
[0161] In a further aspect, the compound has a structure represented by a formula:



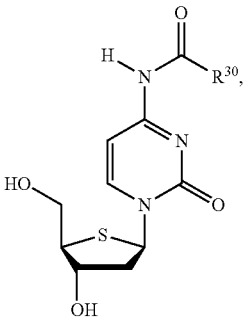
[0162] In a further aspect, the compound has a structure represented by a formula:



[0163] In a further aspect, the compound has a structure represented by a formula:



[0164] In a further aspect, the compound has a structure represented by a formula:



wherein R^{30} is C1-C30 alkyl.

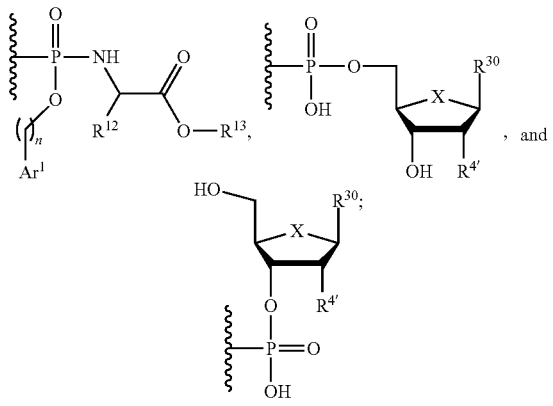
[0165] In one aspect, n is selected from 0, 1, and 2. In a further aspect, n is selected from 0 and 1. In a still further aspect, n is 0. In a still further aspect, n is 1. In yet a further aspect, n is 2.

[0166] a. X Groups

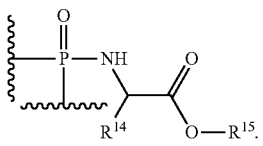
[0167] In one aspect, X, when present, is selected from O and S. In a further aspect, X, when present, is 0. In a still further aspect, X, when present, is S.

[0168] b. R^1 and R^2 Groups

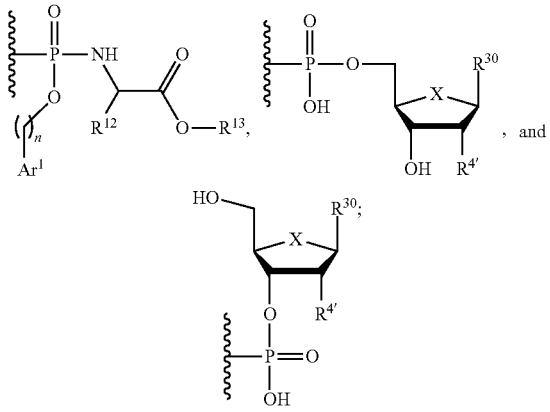
[0169] In one aspect, each of R^1 and R^2 is independently selected from hydrogen, —C(O)R^{10}, —P(O)$(OR^{11})_2$, —P(O)(OH)OP(O)(OH)OP(O)$(OH)_2$, and a structure represented by a formula selected from:



provided that one of R^1 and R^2 is hydrogen, or each of R^1 and R^2 together comprise a structure represented by a formula:

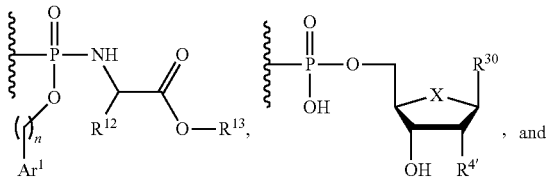


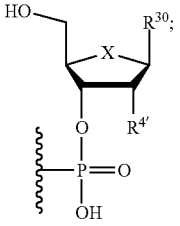
[0170] In a further aspect, each of R^1 and R^2 is independently selected from hydrogen, —C(O)R^{10}, —P(O)$(OR^{11})_2$, —P(O)(OH)OP(O)(OH)OP(O)$(OH)_2$, and a structure represented by a formula selected from:



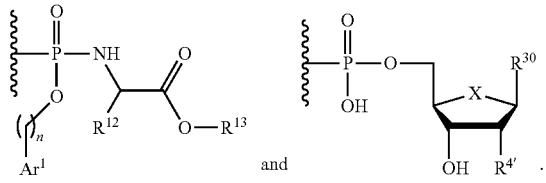
provided that one of R^1 and R^2 is hydrogen.

[0171] In a further aspect, each of R^1 and R^2 is independently selected from hydrogen and a structure represented by a formula selected from:

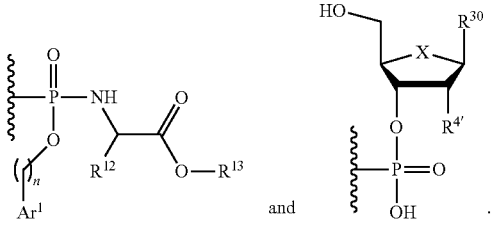




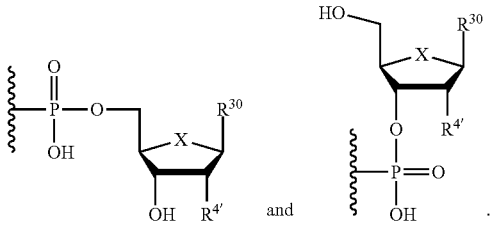
[0172] In a further aspect, each of R^1 and R^2 is independently selected from hydrogen and a structure represented by a formula selected from:



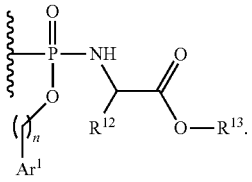
[0173] In a further aspect, each of R^1 and R^2 is independently selected from hydrogen and a structure represented by a formula selected from:



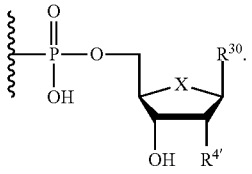
[0174] In a further aspect, each of R^1 and R^2 is independently selected from hydrogen and a structure represented by a formula selected from:



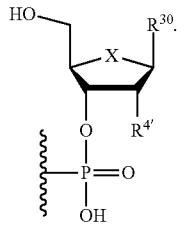
[0175] In a further aspect, each of R^1 and R^2 is independently selected from hydrogen and a structure represented by a formula:



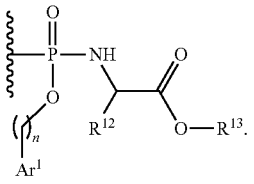
[0176] In a further aspect, each of R^1 and R^2 is independently selected from hydrogen and a structure represented by a formula:



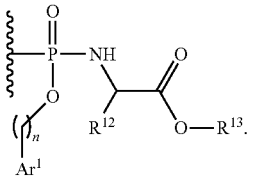
[0177] In a further aspect, each of R^1 and R^2 is independently selected from hydrogen and a structure represented by a formula:



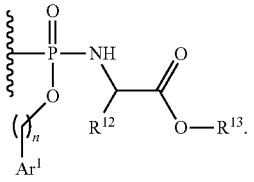
[0178] In a still further aspect, each of R^1 and R^2 is independently selected from hydrogen, —C(O)R^{10} and —P(O)(OR^{11})$_2$. In yet a further aspect, each of R^1 and R^2 is independently selected from hydrogen, —C(O)R^{10}, and a structure represented by a formula:



In an even further aspect, each of R^1 and R^2 is independently selected from hydrogen, —P(O)(OR^{11})$_2$, —P(O)(OH)OP(O)(OH)OP(O)(OH)$_2$, and a structure represented by a formula:

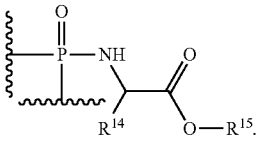


In a still further aspect, each of R^1 and R^2 is independently selected from hydrogen and —C(O)R^{10}. In yet a further aspect, each of R^1 and R^2 is independently selected from hydrogen and —P(O)(OR^{11})$_2$. In an even further aspect, each of R^1 and R^2 is independently selected from hydrogen and a structure represented by a formula:



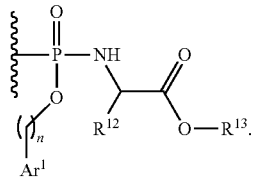
[0179] In a further aspect, each of R^1 and R^2 is independently selected from hydrogen and —P(O)(OH)OP(O)(OH)OP(O)(OH)$_2$.

[0180] In a further aspect, each of R^1 and R^2 together comprise a structure represented by a formula:

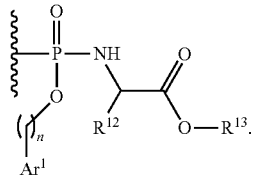


[0181] In a further aspect, each of R^1 and R^2 is hydrogen.

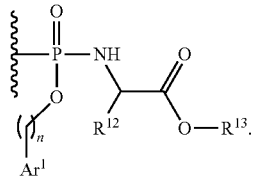
[0182] In a further aspect, R^1 is selected from hydrogen, —C(O)R^{10}, —P(O)(OR^{11})$_2$, —P(O)(OH)OP(O)(OH)OP(O)(OH)$_2$, and a structure represented by a formula:



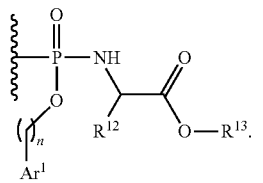
[0183] In a still further aspect, R^1 is selected from hydrogen, —C(O)R^{10}, and —P(O)(OR^{11})$_2$. In yet a further aspect, R^1 is selected from hydrogen, —C(O)R^{10}, and a structure represented by a formula:



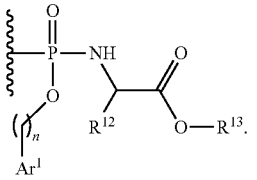
[0184] In an even further aspect, R^1 is selected from hydrogen, —P(O)(OR^{11})$_2$, and a structure represented by a formula:



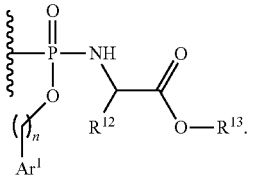
[0185] In a still further aspect, R^1 is selected from hydrogen and —C(O)R^{10}. In yet a further aspect, R^1 is selected from hydrogen and —P(O)(OR^{11})$_2$. In an even further aspect, R^1 is selected from hydrogen and a structure represented by a formula:



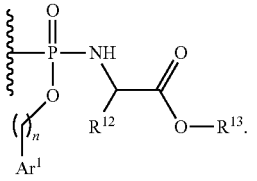
[0186] In a further aspect, R^1 is hydrogen. In a still further aspect, R^1 is —C(O)R^{10}. In yet a further aspect, R^1 is —P(O)(OR^{11})$_2$. In an even further aspect, R^1 is a structure represented by a formula:



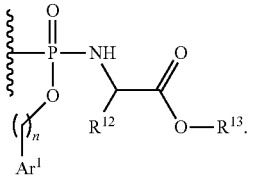
[0187] In a further aspect, R^2 is selected from hydrogen, —C(O)R^{10}, —P(O)(OR^{11})$_2$, and a structure represented by a formula:



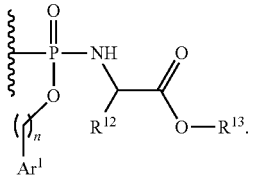
[0188] In a still further aspect, R^2 is selected from hydrogen, —C(O)R^{10}, and —P(O)(OR^{11})$_2$. In yet a further aspect, R^2 is selected from hydrogen, —C(O)R^{10}, and a structure) represented by a formula:



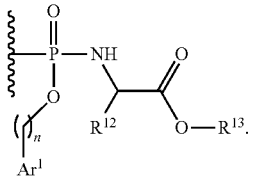
[0189] In an even further aspect, R^2 is selected from hydrogen, —P(O)(OR^{11})$_2$, and a structure represented by a formula:



[0190] In a still further aspect, R^2 is selected from hydrogen and —C(O)R^{10}. In yet a further aspect, R^2 is selected from hydrogen and —P(O)(OR^{11})$_2$. In an even further aspect, R^2 is selected from hydrogen and a structure represented by a formula:



[0191] In a further aspect, R^2 is hydrogen. In a still further aspect, R^2 is —C(O)R^{10}. In yet a further aspect, R^2 is —P(O)(OR^{11})$_2$. In an even further aspect, R^2 is a structure represented by a formula:



[0192] c. R^3 Groups

[0193] In one aspect, R^3 is selected from hydrogen, —C(O)(C1-C30 alkyl), and —C(O)(C2-C30 alkenyl). In a further aspect, R^3 is selected from hydrogen, —C(O)(C1-C15 alkyl), and —C(O)(C2-C15 alkenyl). In a still further aspect, R^3 is selected from hydrogen, —C(O)(C1-C8 alkyl), and —C(O)(C2-C8 alkenyl). In yet a further aspect, R^3 is selected from hydrogen, fluoro, —C(O)(C1-C4 alkyl), and —C(O)(C2-C4 alkenyl). In an even further aspect, R^3 is selected from hydrogen, —C(O)CH_3, —C(O)CH_2CH_3, —C(O)$CH(CH_3)_2$, —C(O)$CH_2CH_2CH_3$, —C(O)$CH{=}CH_2$, —C(O)$C(CH_3){=}CH_2$, —C(O)$CH{=}CHCH_3$, and —C(O)$CH_2CH{=}CH_2$. In a still further aspect, R^3 is selected from hydrogen, —C(O)CH_3, —C(O)CH_2CH_3, —C(O)$CH(CH_3)_2$, —C(O)$CH_2CH_2CH_3$, and —C(O)$CH{=}CH_2$.

[0194] In a further aspect, R^3 is selected from hydrogen and —C(O)(C1-C30 alkyl). In a still further aspect, R^3 is selected from hydrogen and —C(O)(C1-C15 alkyl). In yet a further aspect, R^3 is selected from hydrogen and —C(O)(C1-C8 alkyl). In an even further aspect, R^3 is selected from hydrogen and —C(O)(C1-C4 alkyl). In a still further aspect, R^3 is selected from hydrogen, —C(O)CH_3, —C(O)CH_2CH_3, —C(O)$CH(CH_3)_2$, and —C(O)$CH_2CH_2CH_3$. In yet a further aspect, R^3 is selected from hydrogen, —C(O)CH_3, and —C(O)CH_2CH_3. In an even further aspect, R^3 is selected from hydrogen and —C(O)CH_2CH_3. In a still further aspect, R^3 is selected from hydrogen and —C(O)CH_3.

[0195] In a further aspect, R^3 is selected from hydrogen and —C(O)(C2-C30 alkenyl). In a still further aspect, R^3 is selected from hydrogen and —C(O)(C2-C15 alkenyl). In yet a further aspect, R^3 is selected from hydrogen and —C(O)(C2-C8 alkenyl). In an even further aspect, R^3 is selected from hydrogen and —C(O)(C2-C4 alkenyl). In a still further aspect, R^3 is selected from hydrogen, —C(O)$CH{=}CH_2$, —C(O)$C(CH_3){=}CH_2$, —C(O)$CH{=}CHCH_3$, and —C(O)$CH_2CH{=}CH_2$. In yet a further aspect, R^3 is selected from hydrogen and —C(O)$CH{=}CH_2$.

[0196] In a further aspect, R^3 is selected from —C(O)(C1-C30 alkyl) and —C(O)(C2-C30 alkenyl). In a still further

aspect, R^3 is selected from —C(O)(C1-C15 alkyl) and —C(O)(C2-C15 alkenyl). In yet a further aspect, R^3 is selected from —C(O)(C1-C8 alkyl) and —C(O)(C2-C8 alkenyl). In an even further aspect, R^3 is selected from —C(O)(C1-C4 alkyl) and —C(O)(C2-C4 alkenyl). In a still further aspect, R^3 is selected from —$C(O)CH_3$, —$C(O)CH_2CH_3$, —$C(O)CH(CH_3)_2$, —$C(O)CH_2CH_2CH_3$, —$C(O)CH{=}CH_2$, —$C(O)C(CH_3){=}CH_2$, —$C(O)CH{=}CHCH_3$, and —$C(O)CH_2CH{=}CH_2$. In yet a further aspect, R^3 is selected from —$C(O)CH_3$, —$C(O)CH_2CH_3$, —$C(O)CH(CH_3)_2$, and —$C(O)CH{=}CH_2$.

[0197] In a further aspect, R^3 is —C(O)(C1-C30 alkyl). In a still further aspect, R^3 is —C(O)(C1-C15 alkyl). In yet a further aspect, R^3 is —C(O)(C1-C8 alkyl). In an even further aspect, R^3 is —C(O)(C1-C4 alkyl). In a still further aspect, R^3 is selected from —$C(O)CH_3$, —$C(O)CH_2CH_3$, —$C(O)CH(CH_3)_2$, and —$C(O)CH_2CH_2CH_3$. In yet a further aspect, R^3 is selected from —$C(O)CH_3$ and —$C(O)CH_2CH_3$. In an even further aspect, R^3 is —$C(O)CH_2CH_3$. In a still further aspect, R^3 is —$C(O)CH_3$.

[0198] In a further aspect, R^3 is —C(O)(C2-C30 alkenyl). In a still further aspect, R^3 is —C(O)(C2-C15 alkenyl). In yet a further aspect, R^3 is —C(O)(C2-C8 alkenyl). In an even further aspect, R^3 is —C(O)(C2-C4 alkenyl). In a still further aspect, R^3 is selected from —$C(O)CH{=}CH_2$, —$C(O)C(CH_3){=}CH_2$, —$C(O)CH{=}CHCH_3$, and —$C(O)CH_2CH{=}CH_2$. In yet a further aspect, R^3 is —$C(O)CH{=}CH_2$.

[0199] In a further aspect, R^3 is hydrogen.

[0200] d. R^4 and $R^{4'}$ Groups

[0201] In one aspect, each of R^4 and $R^{4'}$, when present, is independently selected from hydrogen, fluoro, —CN, C2-C4 alkenyl, C2-C4 alkynyl, C1-C4 haloalkyl, and —OR^{16}.

[0202] In a further aspect, each of R^4 and $R^{4'}$, when present, is independently selected from hydrogen and —CN.

[0203] In a further aspect, each of R^4 and $R^{4'}$, when present, is independently selected from hydrogen, C2-C4 alkenyl, C2-C4 alkynyl, and C1-C4 haloalkyl. In a still further aspect, each of R^4 and $R^{4'}$, when present, is independently selected from hydrogen, ethenyl, propenyl, ethynyl, propynyl, —CH_2CF_2, —$CH_2CH_2CF_2$, —$CH(CH_3)CH_2CF_2$, and —$CH_2CH_2CH_2CF_2$. In yet a further aspect, each of R^4 and $R^{4'}$, when present, is independently selected from hydrogen, ethenyl, ethynyl, —CH_2CF_2, and —$CH_2CH_2CF_2$. In an even further aspect, each of R^4 and $R^{4'}$, when present, is independently selected from hydrogen and —CH_2CF_2.

[0204] In a still further aspect, each of R^4 and $R^{4'}$, when present, is independently selected from hydrogen and —OR^{16}. In yet a further aspect, each of R^4 and $R^{4'}$, when present, is independently selected from fluoro and —OR^{16}. In an even further aspect, each of R^4 and $R^{4'}$, when present, is independently selected from hydrogen and fluoro. In a still further aspect, each of R^4 and $R^{4'}$, when present, is fluoro. In yet a further aspect, each of R^4 and $R^{4'}$, when present, is —OR^{16}. In an even further aspect, each of R^4 and $R^{4'}$, when present, is hydrogen.

[0205] e. R^{10} Groups

[0206] In one aspect, R^{10}, when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and —$CH(NH_2)R^{20}$. In a further aspect, R^{10}, when present, is selected from C1-C15 alkyl, C2-C15 alkenyl, and —$CH(NH_2)R^{20}$. In a still further aspect, R^{10}, when present, is selected from C1-C8 alkyl, C2-C8 alkenyl, and —$CH(NH_2)R^{20}$. In yet a further aspect, R^{10}, when present, is selected from C1-C4 alkyl, C2-C4 alkenyl, and —$CH(NH_2)R^{20}$. In an even further aspect, R^{10}, when present, is selected from methyl, ethyl, isopropyl, n-propyl, ethenyl, propenyl, and —$CH(NH_2)R^{20}$. In a still further aspect, R^{10}, when present, is selected from methyl, ethyl, isopropyl, ethenyl, and —$CH(NH_2)R^{20}$. In yet a further aspect, R^{10}, when present, is selected from methyl and —$CH(NH_2)R^{20}$.

[0207] In a further aspect, R^{10}, when present, is selected from C1-C30 alkyl and C2-C30 alkenyl. In a still further aspect, R^{10}, when present, is selected from C1-C15 alkyl and C2-C15 alkenyl. In yet a further aspect, R^{10}, when present, is selected from C1-C8 alkyl and C2-C8 alkenyl. In an even further aspect, R^{10}, when present, is selected from C1-C4 alkyl and C2-C4 alkenyl. In a still further aspect, R^{10}, when present, is selected from methyl, ethyl, isopropyl, n-propyl, ethenyl, and isopropenyl. In yet a further aspect, R^{10}, when present, is selected from methyl, ethyl, and ethenyl.

[0208] In a further aspect, R^{10}, when present, is selected from C1-C30 alkyl and —$CH(NH_2)R^{20}$. In a still further aspect, R^{10}, when present, is selected from C1-C15 alkyl and —$CH(NH_2)R^{20}$. In yet a further aspect, R^{10}, when present, is selected from C1-C8 alkyl and —$CH(NH_2)R^{20}$. In an even further aspect, R^{10}, when present, is selected from C1-C4 alkyl and —$CH(NH_2)R^{20}$. In a still further aspect, R^{10}, when present, is selected from methyl, ethyl, isopropyl, n-propyl, and —$CH(NH_2)R^{20}$. In yet a further aspect, R^{10}, when present, is selected from methyl, ethyl, and —$CH(NH_2)R^{20}$. In an even further aspect, R^{10}, when present, is selected from methyl and —$CH(NH_2)R^{20}$.

[0209] In a further aspect, R^{10}, when present, is selected from C2-C30 alkenyl and —$CH(NH_2)R^{20}$. In a still further aspect, R^{10}, when present, is selected from C2-C15 alkenyl and —$CH(NH_2)R^{20}$. In yet a further aspect, R^{10}, when present, is selected from C2-C8 alkenyl and —$CH(NH_2)R^{20}$. In an even further aspect, R^{10}, when present, is selected from C2-C4 alkenyl and —$CH(NH_2)R^{20}$. In a still further aspect, R^{10}, when present, is selected from ethyenyl, propenyl, and —$CH(NH_2)R^{20}$. In yet a further aspect, R^{10}, when present, is selected from ethyenyl and —$CH(NH_2)R^{20}$.

[0210] In a further aspect, R^{10}, when present, is C1-C30 alkyl. In a still further aspect, R^{10}, when present, is C1-C15 alkyl. In yet a further aspect, R^{10}, when present, is C1-C8 alkyl. In an even further aspect, R^{10}, when present, is C1-C4 alkyl. In a still further aspect, R^{10}, when present, is selected from methyl, ethyl, isopropyl, and n-propyl. In yet a further aspect, R^{10}, when present, is selected from methyl and ethyl. In an even further aspect, R^{10}, when present, is ethyl. In a still further aspect, R^{10}, when present, is methyl.

[0211] In a further aspect, R^{10}, when present, is C2-C30 alkenyl. In a still further aspect, R^{10}, when present, is C2-C15 alkenyl. In yet a further aspect, R^{10}, when present, is C2-C8 alkenyl. In an even further aspect, R^{10}, when present, is C2-C4 alkenyl. In a still further aspect, R^{10}, when present, is selected from ethyenyl and propenyl. In yet a further aspect, R^{10}, when present, is propenyl. In an even further aspect, R^{10}, when present, is ethyenyl.

[0212] In a further aspect, R^{10}, when present, is —$CH(NH_2)R^{20}$.

[0213] f. R^{11} Groups

[0214] In one aspect, each occurrence of R^{11}, when present, is independently selected from hydrogen, —(C1-C10 alkyl)CO_2(C1-C10 alkyl), —(C1-C10 alkoxy)CO_2(C1-C10 alkyl), —(C1-C10 alkyl)CO_2(C1-C10 alkylthio), —(C1-

C10 alkyl)-S—S—(C1-C10 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In a further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —(C1-C8 alkyl)CO_2(C1-C8 alkyl), —(C1-C8 alkoxy)CO_2(C1-C8 alkyl), —(C1-C8 alkyl)CO_2(C1-C8 alkylthio), —(C1-C8 alkyl)-S—S—(C1-C8 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In a still further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —(C1-C4 alkyl)CO_2(C1-C4 alkyl), —(C1-C4 alkoxy)CO_2(C1-C4 alkyl), —(C1-C4 alkyl)CO_2(C1-C4 alkylthio), —(C1-C4 alkyl)-S—S—(C1-C4 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In yet a further aspect, each occurrence of R^{11}, when present, is independently selected from hydrogen, —$CH_2CO_2CH_3$, —$CH_2CO_2CH_2CH_3$, —$CH_2CO_2CH_2CH_2CH_3$, —$CH_2CO_2CH(CH_3)_2$, —$OCH_2CO_2CH_3$, —$OCH_2CO_2CH_2CH_3$, —$OCH_2CO_2CH_2CH_2CH_3$, —$OCH_2CO_2CH(CH_3)_2$, —$CH_2CO_2CH_2SH$, —$CH_2CO_2CH_2CH_2SH$, —$CH_2CO_2CH_2CH_2CH_2SH$, —$CH_2CO_2CH(CH_3)CH_2SH$, —CH_2—S—S—CH_3, —CH_2—S—S—CH_2CH_3, —CH_2—S—S—$CH_2CH_2CH_3$, —CH_2—S—S—$CH(CH_3)_2$, and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In an even further aspect, each occurrence of R^{11}, when present, is independently selected from hydrogen, —$CH_2CO_2CH_3$, —$CH_2CO_2CH_2CH_3$, —$OCH_2CO_2CH_3$, —$OCH_2CO_2CH_2CH_3$, —$CH_2CO_2CH_2SH$, —$CH_2CO_2CH_2CH_2SH$, —CH_2—S—S—CH_3, —CH_2—S—S—CH_2CH_3, and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In a still further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —$CH_2CO_2CH_3$, —$OCH_2CO_2CH_3$, —$CH_2CO_2CH_2SH$, —CH_2—S—S—CH_3, and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH.

[0215] In a further aspect, each occurrence of R^{11}, when present, is independently selected from hydrogen, —(C1-C10 alkyl)CO_2(C1-C10 alkyl), —(C1-C10 alkyl)-S—S—(C1-C10 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In a still further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —(C1-C8 alkyl)CO_2(C1-C8 alkyl), —(C1-C8 alkyl)-S—S—(C1-C8 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In yet a further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —(C1-C4 alkyl)CO_2(C1-C4 alkyl), —(C1-C4 alkyl)-S—S—(C1-C4 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In an even further aspect, each occurrence of R^{11}, when present, is independently selected from hydrogen, —$CH_2CO_2CH_3$, —$CH_2CO_2CH_2CH_3$, —$CH_2CO_2CH_2CH_2CH_3$, —$CH_2CO_2CH(CH_3)_2$, —CH_2—S—S—CH_3, —CH_2—S—S—CH_2CH_3, —CH_2—S—S—$CH_2CH_2CH_3$, —CH_2—S—S—$CH(CH_3)_2$, and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In a still further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —$CH_2CO_2CH_3$, —$CH_2CO_2CH_2CH_3$, —CH_2—S—S—CH_3, —CH_2—S—S—CH_2CH_3, and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In yet a further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —$CH_2CO_2CH_3$, —CH_2—S—S—CH_3, and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH.

[0216] In a further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —(C1-C10 alkoxy)CO_2(C1-C10 alkyl), —(C1-C10 alkyl)CO_2(C1-C10 alkylthio), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In a still further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —(C1-C8 alkoxy)CO_2(C1-C8 alkyl), —(C1-C8 alkyl)CO_2(C1-C8 alkylthio), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In yet a further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —(C1-C4 alkoxy)CO_2(C1-C4 alkyl), —(C1-C4 alkyl)CO_2(C1-C4 alkylthio), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In an even further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —$OCH_2CO_2CH_3$, —$OCH_2CO_2CH_2CH_3$, —$OCH_2CO_2CH_2CH_2CH_3$, —$OCH_2CO_2CH(CH_3)_2$, —$CH_2CO_2CH_2SH$, —$CH_2CO_2CH_2CH_2SH$, —$CH_2CO_2CH_2CH_2CH_2SH$, —$CH_2CO_2CH(CH_3)CH_2SH$, and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In a still further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —$OCH_2CO_2CH_3$, —$OCH_2CO_2CH_2CH_3$, —$CH_2CO_2CH_2SH$, —$CH_2CO_2CH_2CH_2SH$, and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In yet a further aspect, each occurrence of R^{11}, when present, is independently selected from hydrogen, —$OCH_2CO_2CH_3$, —$CH_2CO_2CH_2SH$, and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH.

[0217] In a further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —(C1-C10 alkyl)CO_2(C1-C10 alkyl), —(C1-C10 alkoxy)CO_2(C1-C10 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In a still further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —(C1-C8 alkyl)CO_2(C1-C8 alkyl), —(C1-C8 alkoxy)CO_2(C1-C8 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In yet a further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —(C1-C4 alkyl)CO_2(C1-C4 alkyl), —(C1-C4 alkoxy)CO_2(C1-C4 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In an even further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —$CH_2CO_2CH_3$, —$CH_2CO_2CH_2CH_3$, —$CH_2CO_2CH_2CH_2CH_3$,

—$CH_2CO_2CH(CH_3)_2$, —$OCH_2CO_2CH_3$, —$OCH_2CO_2CH_2CH_3$, —$OCH_2CO_2CH_2CH_2CH_3$, —$OCH_2CO_2CH(CH_3)_2$, and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In a still further aspect, each occurrence of R^{11}, when present, is independently selected from hydrogen, —$CH_2CO_2CH_3$, —$CH_2CO_2CH_2CH_3$, —$OCH_2CO_2CH_3$, —$OCH_2CO_2CH_2CH_3$, and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In yet a further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —$CH_2CO_2CH_3$, —$OCH_2CO_2CH_3$, and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH.

[0218] In a further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —(C1-C10 alkyl)CO_2(C1-C10 alkylthio), —(C1-C10 alkyl)-S—S—(C1-C10 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In a still further aspect, each occurrence of R^{11}, when present, is independently selected from hydrogen, —(C1-C8 alkyl)CO_2(C1-C8 alkylthio), —(C1-C8 alkyl)-S—S—(C1-C8 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In yet a further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —(C1-C4 alkyl)CO_2(C1-C4 alkylthio), —(C1-C4 alkyl)-S—S—(C1-C4 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In an even further aspect, each occurrence of R^{11}, when present, is independently selected from hydrogen, —$CH_2CO_2CH_2SH$, —$CH_2CO_2CH_2CH_2SH$, —$CH_2CO_2CH_2CH_2CH_2SH$, —$CH_2CO_2CH(CH_3)CH_2SH$, —CH_2—S—S—CH_3, —CH_2—S—S—CH_2CH_3, —CH_2—S—S—$CH_2CH_2CH_3$, —CH_2—S—S—$CH(CH_3)_2$, and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In a still further aspect, each occurrence of R^{11}, when present, is independently selected from hydrogen, —$CH_2CO_2CH_2SH$, —$CH_2CO_2CH_2CH_2SH$, —CH_2—S—S—CH_3, —CH_2—S—S—CH_2CH_3, and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH. In yet a further aspect, each occurrence of R^{11}, when present, is independently selected from hydrogen, —$CH_2CO_2CH_2SH$, —CH_2—S—S—CH_3, and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH.

[0219] In a further aspect, each occurrence of RH, when present, is independently selected from hydrogen, —(C1-C10 alkyl)CO_2(C1-C10 alkyl), —(C1-C10 alkoxy)CO_2(C1-C10 alkyl), —(C1-C10 alkyl)CO_2(C1-C10 alkylthio), —(C1-C10 alkyl)-S—S—(C1-C10 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, or 2 groups independently selected from halogen and —OH. In a still further aspect, each occurrence of R^{11}, when present, is independently selected from hydrogen, —(C1-C10 alkyl)CO_2(C1-C10 alkyl), —(C1-C10 alkoxy)CO_2(C1-C10 alkyl), —(C1-C10 alkyl)CO_2(C1-C10 alkylthio), —(C1-C10 alkyl)-S—S—(C1-C10 alkyl), and Ar^2, and wherein each alkyl is substituted with 0 or 1 group selected from halogen and —OH. In yet a further aspect, each occurrence of R^{11}, when present, is independently selected from hydrogen, —(C1-C10 alkyl)CO_2(C1-C10 alkyl), —(C1-C10 alkoxy)CO_2(C1-C10 alkyl), —(C1-C10 alkyl)CO_2(C1-C10 alkylthio), —(C1-C10 alkyl)-S—S—(C1-C10 alkyl), and Ar^2, and wherein each alkyl is monosubstituted with a group selected from halogen and —OH. In an even further aspect, each occurrence of R^{11}, when present, is independently selected from hydrogen, —(C1-C10 alkyl)CO_2(C1-C10 alkyl), —(C1-C10 alkoxy)CO_2(C1-C10 alkyl), —(C1-C10 alkyl)CO_2(C1-C10 alkylthio), —(C1-C10 alkyl)-S—S—(C1-C10 alkyl), and Ar^2, and wherein each alkyl is unsubstituted.

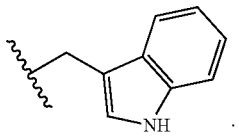
[0220] In a further aspect, each occurrence of R^{11}, when present, is hydrogen.

[0221] g. R^{12} Groups

[0222] In one aspect, R^{12}, when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylamino, —(C1-C8)C(O)NH_2, aryl, and —(CH_2)aryl. In a further aspect, R^{12}, when present, is selected from hydrogen, C1-C4 alkyl, C1-C4 hydroxyalkyl, C1-C4 alkylamino, —(C1-C4)C(O)NH_2, aryl, and —(CH_2)aryl. In a still further aspect, R^{12}, when present, is selected from hydrogen, methyl, ethyl, isopropyl, n-propyl, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)CH_2OH$, —$CH_2CH_2CH_2OH$, —CH_2NH_2, —$CH_2CH_2NH_2$, —$CH(CH_3)CH_2NH_2$, —$CH_2CH_2CH_2NH_2$, —$CH_2C(O)NH_2$, —$CH_2CH_2C(O)NH_2$, —$CH(CH_3)CH_2C(O)NH_2$, —$CH_2CH_2CH_2C(O)NH_2$, aryl, and —(CH_2)aryl. In yet a further aspect, R^{12}, when present, is selected from hydrogen, methyl, ethyl, isopropyl, n-propyl, —CH_2OH, —CH_2CH_2OH, —CH_2NH_2, —$CH_2CH_2NH_2$, —$CH_2C(O)NH_2$, —$CH_2CH_2C(O)NH_2$, aryl, and —(CH_2)aryl. In an even further aspect, R^{12}, when present, is selected from hydrogen, methyl, ethyl, isopropyl, n-propyl, —CH_2OH, —CH_2NH_2, —$CH_2C(O)NH_2$, aryl, and —(CH_2)aryl.

[0223] In a further aspect, R^{12}, when present, is selected from hydrogen, aryl, and —(CH_2)aryl. In a still further aspect, R^{12}, when present, is selected from hydrogen and aryl. In yet a further aspect, R^{12}, when present, is selected from hydrogen and —(CH_2)aryl. In an even further aspect, R^{12}, when present, is selected from aryl and —(CH_2)aryl. In a still further aspect, R^{12}, when present, is aryl. In yet a further aspect, R^{12}, when present, is —(CH_2)aryl.

[0224] In a further aspect, R^{12}, when present, is selected from hydrogen, phenyl, and a structure



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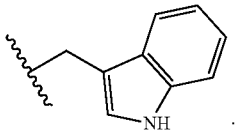
In a still further aspect, R^{12}, when present, is selected from hydrogen and phenyl. In yet a further aspect, R^{12}, when present, is selected from hydrogen and a structure



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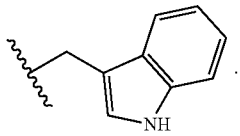
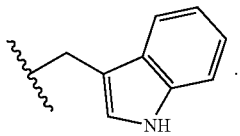
In an even further aspect, R^{12}, when present, is selected from phenyl and a structure



In a still further aspect, R^{12}, when present, is phenyl. In yet a further aspect, R^{12}, when present, is a structure



[0225] In a further aspect, R^{12}, when present, is selected from hydrogen, C1-C8 hydroxyalkyl, and C1-C8 alkylamino. In a still further aspect, R^{12}, when present, is selected from hydrogen, C1-C4 hydroxyalkyl, and C1-C4 alkylamino. In yet a further aspect, R^{12}, when present, is selected from hydrogen, —CH_2OH, —CH_2CH_2OH, —$CH(CH_3)CH_2OH$, —$CH_2CH_2CH_2OH$, —CH_2NH_2, —$CH_2CH_2NH_2$, —$CH(CH_3)CH_2NH_2$, and —$CH_2CH_2CH_2NH_2$. In an even further aspect, R^{12}, when present, is selected from hydrogen, —CH_2OH, —CH_2CH_2OH, —CH_2NH_2, and —$CH_2CH_2NH_2$. In a still further aspect, R^{12}, when present, is selected from hydrogen, —CH_2OH, and —CH_2NH_2. In yet a further aspect, R^{12}, when present, is selected from hydrogen, —CH_2OH, and —$(CH_2)_4NH_2$. In an even further aspect, R^{12}, when present, is selected from hydrogen and —CH_2OH. In a still further aspect, R^{12}, when present, is selected from hydrogen and —$(CH_2)_4NH_2$. In yet a further aspect, R^{12}, when present, is —CH_2OH. In an even further aspect, R^{12}, when present, is —$(CH_2)_4NH_2$.

[0226] In a further aspect, R^{12}, when present, is selected from hydrogen and —(C1-C8)$C(O)NH_2$. In a still further aspect, R^{12}, when present, is selected from hydrogen and —(C1-C4)$C(O)NH_2$. In yet a further aspect, R^{12}, when present, is selected from hydrogen, —$CH_2C(O)NH_2$, —$CH_2CH_2C(O)NH_2$, —$CH(CH_3)CH_2C(O)NH_2$, and —$CH_2CH_2CH_2C(O)NH_2$. In an even further aspect, R^{12}, when present, is selected from hydrogen, —$CH_2C(O)NH_2$, and —$CH_2CH_2C(O)NH_2$. In a still further aspect, R^{12}, when present, is selected from hydrogen and —$CH_2C(O)NH_2$. In yet a further aspect, R^{12}, when present, is selected from hydrogen and $CH_2CH_2C(O)NH_2$. In an even further aspect, R^{12}, when present, is $CH_2CH_2C(O)NH_2$.

[0227] In one aspect, R^{12}, when present, is selected from hydrogen and C1-C8 alkyl. In a further aspect, R^{12}, when present, is selected from hydrogen and C1-C4 alkyl. In a still further aspect, R^{12}, when present, is selected from hydrogen, methyl, ethyl, isopropyl, and n-propyl. In yet a further aspect, R^{12}, when present, is selected from hydrogen, methyl, and ethyl. In an even further aspect, R^{12}, when present, is selected from hydrogen and ethyl. In a still further aspect, R^{12}, when present, is selected from hydrogen and methyl.

[0228] In a further aspect, R^{12}, when present, is C1-C8 alkyl. In a still further aspect, R^{12}, when present, is selected from methyl, ethyl, isopropyl, n-propyl, isobutyl, sec-butyl, tertbutyl, and n-butyl. In yet a further aspect, R^{12}, when present, is selected from methyl, ethyl, isopropyl, and n-propyl. In an even further aspect, R^{12}, when present, is selected from methyl and ethyl. In a still further aspect, R^{12}, when present, is ethyl. In yet a further aspect, R^{12}, when present, is methyl.

[0229] In a further aspect, R^{12}, when present, is hydrogen.

[0230] h. R^{13} Groups

[0231] In one aspect, R^{13}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar^3. In a further aspect, R^{13}, when present, is selected from C1-C8 alkyl, C3-C8 cycloalkyl, and Ar^3. a still further aspect, R^{13}, when present, is selected from C1-C4 alkyl, C3-C6 cycloalkyl, and Ar^3. In yet a further aspect, R^{13}, when present, is selected from methyl, ethyl, isopropyl, n-propyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and Ar^3.

[0232] In a further aspect, R^{13}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar^3. In an even further aspect, R^{13}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar^3.

[0233] In a further aspect, R^{13}, when present, is selected from C1-C10 alkyl and C3-C10 cycloalkyl. In a still further aspect, R^{13}, when present, is selected from C1-C8 alkyl and C3-C8 cycloalkyl. In yet a further aspect, R^{13}, when present, is selected from C1-C4 alkyl and C3-C6 cycloalkyl. In an even further aspect, R^{13}, when present, is selected from methyl, ethyl, 2-ethylbutyl, isopropyl, n-propyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0234] In a further aspect, R^{13}, when present, is selected from C3-C10 cycloalkyl and Ar^3. In a still further aspect, R^{13}, when present, is selected from C3-C8 cycloalkyl and Ar^3. In yet a further aspect, R^{13}, when present, is selected from C3-C6 cycloalkyl and Ar^3. In an even further aspect, R^{13}, when present, is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and Ar^3.

[0235] In a further aspect, R^{13}, when present, is C1-C10 alkyl. In a still further aspect, R^{13}, when present, is C1-C8 alkyl. In yet a further aspect, R^{13}, when present, is C1-C4 alkyl. In an even further aspect, R^{13}, when present, is selected from 2-ethylbutyl, methyl, ethyl, isopropyl, and n-propyl. In a still further aspect, R^{13}, when present, is selected from 2-ethylbutyl, methyl, and ethyl. In yet a further aspect, R^{13}, when present, is selected from 2-ethylbutyl and ethyl. In an even further aspect, R^{13}, when present, is selected from 2-ethylbutyl and methyl. In a still further aspect, R^{13}, when present, is 2-ethylbutyl.

[0236] In a further aspect, R^{13}, when present, is C3-C10 cycloalkyl. In a still further aspect, R^{13}, when present, is C3-C8 cycloalkyl. In yet a further aspect, R^{13}, when present, is selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. In an even further aspect, R^{13}, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl. In a still further aspect, R^{13}, when present, is selected from cyclopropyl and cyclobutyl. In yet a further aspect, R^{13}, when present, is cyclohexyl. In an even further aspect, R^{13}, when present, is cyclopentyl. In a still further aspect, R^{13}, when present, is cyclobutyl. In yet a further aspect, R^{13}, when present, is cyclopropyl.

[0237] In a further aspect, R^{13}, when present, is Ar^3.

[0238] In a further aspect, R^{13}, when present, is aryl substituted with 0 or 1 C1-C10 alkyl group. In a still further

aspect, R^{13}, when present, is aryl substituted with 0 or 1 C1-C8 alkyl group. In yet a further aspect, R^{13}, when present, is aryl substituted with 0 or 1 C1-C4 alkyl group. In an even further aspect, R^{13}, when present, is aryl substituted with 0 or 1 group selected from methyl, ethyl, isopropyl, and n-propyl. In a still further aspect, R^{13}, when present, is aryl substituted with 0 or 1 group selected from methyl and ethyl. In yet a further aspect, R^{13}, when present, is aryl substituted with 0 or 1 ethyl group. In an even further aspect, R^{13}, when present, is aryl substituted with 0 or 1 methyl group.

[0239] In a further aspect, R^{13}, when present, is phenyl substituted with 0 or 1 C1-C10 alkyl group. In a still further aspect, R^{13}, when present, is phenyl substituted with 0 or 1 C1-C8 alkyl group. In yet a further aspect, R^{13}, when present, is phenyl substituted with 0 or 1 C1-C4 alkyl group. In an even further aspect, R^{13}, when present, is phenyl substituted with 0 or 1 group selected from methyl, ethyl, isopropyl, and n-propyl. In a still further aspect, R^{13}, when present, is phenyl substituted with 0 or 1 group selected from methyl and ethyl. In yet a further aspect, R^{13}, when present, is phenyl substituted with 0 or 1 ethyl group. In an even further aspect, R^{13}, when present, is phenyl substituted with 0 or 1 methyl group.

[0240] i. R^{14} Groups

[0241] In one aspect, R^{14}, when present, is C1-C8 alkyl. In a further aspect, R^{14}, when present, is selected from methyl, ethyl, isopropyl, n-propyl, isobutyl, sec-butyl, tert-butyl, and n-butyl. In a still further aspect, R^{14}, when present, is selected from methyl, ethyl, isopropyl, and n-propyl. In yet a further aspect, R^{14}, when present, is selected from methyl and ethyl. In an even further aspect, R^{14}, when present, is ethyl. In a still further aspect, R^{14}, when present, is methyl.

[0242] j. R^{15} Groups

[0243] In one aspect, R^{15}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and aryl substituted with 0 or 1 C1-C10 alkyl groups. In a further aspect, R'5, when present, is selected from C1-C8 alkyl, C3-C8 cycloalkyl, and aryl substituted with 0 or 1 C1-C10 alkyl group. In a still further aspect, R^{15}, when present, is selected from C1-C4 alkyl, C3-C6 cycloalkyl, and aryl substituted with 0 or 1 C1-C10 alkyl group. In yet a further aspect, R^{15}, when present, is selected from methyl, ethyl, isopropyl, n-propyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and phenyl substituted with 0 or 1 C1-C10 alkyl group.

[0244] In a further aspect, R^{15}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and aryl monosubstituted with a C1-C10 alkyl group. In an even further aspect, R^{15}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and unsubstituted aryl.

[0245] In a further aspect, R^{15}, when present, is selected from C1-C10 alkyl and C3-C10 cycloalkyl. In a still further aspect, R^{15}, when present, is selected from C1-C8 alkyl and C3-C8 cycloalkyl. In yet a further aspect, R^{15}, when present, is selected from C1-C4 alkyl and C3-C6 cycloalkyl. In an even further aspect, R^{15}, when present, is selected from methyl, ethyl, isopropyl, n-propyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0246] In a further aspect, R^{15}, when present, is selected from C3-C10 cycloalkyl and aryl substituted with 0 or 1 C1-C10 alkyl group. In a still further aspect, R^{15}, when present, is selected from C3-C8 cycloalkyl and aryl substituted with 0 or 1 C1-C10 alkyl group. In yet a further aspect, R^{15}, when present, is selected from C3-C6 cycloalkyl and aryl substituted with 0 or 1 C1-C10 alkyl group. In an even further aspect, R^{15}, when present, is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and aryl substituted with 0 or 1 C1-C10 alkyl group.

[0247] In a further aspect, R^{15}, when present, is C1-C10 alkyl. In a still further aspect, R^{15}, when present, is C1-C8 alkyl. In yet a further aspect, R^{15}, when present, is C1-C4 alkyl. In an even further aspect, R^{15}, when present, is selected from methyl, ethyl, isopropyl, and n-propyl. In a still further aspect, R^{15}, when present, is selected from methyl and ethyl. In yet a further aspect, R^{15}, when present, is ethyl. In an even further aspect, R'5, when present, is methyl.

[0248] In a further aspect, R^{15}, when present, is C3-C10 cycloalkyl. In a still further aspect, R^{15}, when present, is C3-C8 cycloalkyl. In yet a further aspect, R^{15}, when present, is selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. In an even further aspect, R^{15}, when present, is selected from cyclopropyl, cyclobutyl, and cyclopentyl. In a still further aspect, R^{15}, when present, is selected from cyclopropyl and cyclobutyl. In yet a further aspect, R^{15}, when present, is cyclohexyl. In an even further aspect, R^{15}, when present, is cyclopentyl. In a still further aspect, R^{15}, when present, is cyclobutyl. In yet a further aspect, R^{15}, when present, is cyclopropyl.

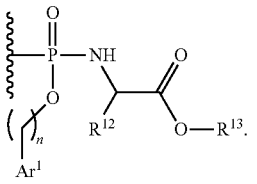
[0249] In a further aspect, R^{15}, when present, is aryl substituted with 0 or 1 C1-C10 alkyl group. In a still further aspect, R^{15}, when present, is aryl substituted with 0 or 1 C1-C8 alkyl group. In yet a further aspect, R^{15}, when present, is aryl substituted with 0 or 1 C1-C4 alkyl group. In an even further aspect, R^{15}, when present, is aryl substituted with 0 or 1 group selected from methyl, ethyl, isopropyl, and n-propyl. In a still further aspect, R^{15}, when present, is aryl substituted with 0 or 1 group selected from methyl and ethyl. In yet a further aspect, R^{15}, when present, is aryl substituted with 0 or 1 ethyl group. In an even further aspect, R^{15}, when present, is aryl substituted with 0 or 1 methyl group.

[0250] In a further aspect, R^{15}, when present, is phenyl substituted with 0 or 1 C1-C10 alkyl group. In a still further aspect, R^{15}, when present, is phenyl substituted with 0 or 1 C1-C8 alkyl group. In yet a further aspect, R^{15}, when present, is phenyl substituted with 0 or 1 C1-C4 alkyl group. In an even further aspect, R^{15}, when present, is phenyl substituted with 0 or 1 group selected from methyl, ethyl, isopropyl, and n-propyl. In a still further aspect, R^{15}, when present, is phenyl substituted with 0 or 1 group selected from methyl and ethyl. In yet a further aspect, R^{15}, when present, is phenyl substituted with 0 or 1 ethyl group. In an even further aspect, R^{15}, when present, is phenyl substituted with 0 or 1 methyl group.

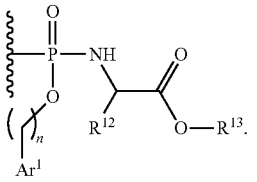
[0251] k. R^{16} Groups

[0252] In one aspect, R^{16}, when present, is selected from hydrogen, methyl, and —C(O)R^{10}. In a further aspect, R^{16}, when present, is selected from hydrogen and methyl. In a still further aspect, R^{16}, when present, is selected from hydrogen and —C(O)R^{16}.

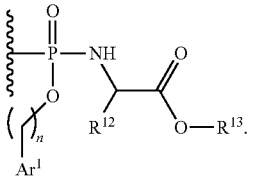
[0253] In a further aspect, R^{16}, when present, is selected from hydrogen, methyl, —C(O)R^{10}, and a structure represented by a formula:



In a still further aspect, R^{16}, when present, is selected from hydrogen and a structure represented by a formula:

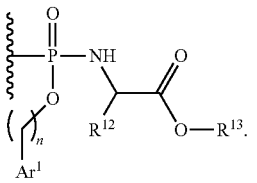


[0254] In yet a further aspect, R^{16}, when present, is selected from hydrogen and —C(O)R^{10}. In an even further aspect, R^{16}, when present, is a structure represented by a formula:



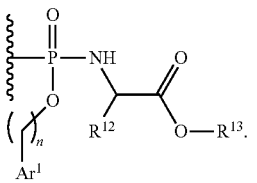
In a still further aspect, R^{16}, when present, is —C(O)R^{10}.

[0255] In a further aspect, R^{16}, when present, is selected from hydrogen, —P(O)(OR^{11})$_2$, and a structure represented by a formula:

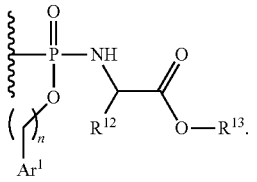


In a still further aspect, R^{16}, when present, is selected from hydrogen and —P(O)(OR^{11})$_2$. In yet a further aspect, R^{16}, when present, is —P(O)(OR^{11})$_2$.

[0256] In a further aspect, R^{16}, when present, is selected from —C(O)R^{16}, —P(O)(OR^{11})$_2$, and a structure represented by a formula:



In a still further aspect, R^{16}, when present, is selected from —C(O)R^{16} and a structure represented by a formula:



In yet a further aspect, R^{16}, when present, is selected from —C(O)R^{16} and —P(O)(OR^{11})$_2$.

[0257] In a further aspect, R^{16}, when present, is selected from hydrogen and methyl. In a still further aspect, R^{16}, when present, is methyl. In yet a further aspect, R^{16}, when present, is hydrogen.

[0258] 1. R^{20} Groups

[0259] In one aspect, R^{20}, when present, is selected from hydrogen, methyl, isopropyl, isobutyl, sec-butyl, —$(CH_2)_3NHC(NH)NH_2$, —$(CH_2)_4NH_2$, —CH_2CO_2H, —$(CH_2)_2CO_2H$, —CH_2OH, —$CH(OH)CH_3$, —$CH_2C(O)NH_2$, —$(CH_2)_2C(O)NH_2$, —CH_2SH, —$(CH_2)_2SCH_3$, —CH_2SeH, —$CH_2C_6H_5$, and —CH_2Cy^1. In a further aspect, R^{20}, when present, is selected from hydrogen, methyl, isopropyl, isobutyl, sec-butyl, —$(CH_2)_3NHC(NH)NH_2$, —$(CH_2)_4NH_2$, —CH_2CO_2H, —$(CH_2)_2CO_2H$, —CH_2OH, —$CH(OH)CH_3$, —$CH_2C(O)NH_2$, —$(CH_2)_2C(O)NH_2$, —CH_2SH, —$(CH_2)_2SCH_3$, —$CH_2C_6H_5$, and —CH_2Cy^1. In a still further aspect, R^{20}, when present, is selected from hydrogen, methyl, isopropyl, isobutyl, sec-butyl, —$(CH_2)_3NHC(NH)NH_2$, —$(CH_2)_4NH_2$, —CH_2CO_2H, —$(CH_2)_2CO_2H$, —CH_2OH, —$CH(OH)CH_3$, —$CH_2C(O)NH_2$, —$(CH_2)_2C(O)NH_2$, —$CH_2C_6H_5$, and —CH_2Cy^1.

[0260] In a further aspect, R^{20}, when present, is selected from hydrogen, methyl, isopropyl, isobutyl, sec-butyl, —$CH_2C_6H_5$, and —CH_2Cy^1. In a still further aspect, R^{20}, when present, is selected from hydrogen, methyl, isopropyl, —$CH_2C_6H_5$, and —CH_2Cy^1. In yet a further aspect, R^{20}, when present, is selected from hydrogen, methyl, —$CH_2C_6H_5$, and —CH_2Cy^1. In an even further aspect, R^{20}, when present, is selected from hydrogen, —$CH_2C_6H_5$, and —CH_2Cy^1. In a still further aspect, R^{20}, when present, is selected from hydrogen and —$CH_2C_6H_5$. In yet a further aspect, R^{20}, when present, is selected from hydrogen and —CH_2Cy^1.

[0261] In a further aspect, R^{20}, when present, is selected from methyl, isopropyl, isobutyl, and sec-butyl. In a still further aspect, R^{20}, when present, is selected from methyl and isopropyl. In yet a further aspect, R^{20}, when present, is sec-butyl. In an even further aspect, R^{20}, when present, is isobutyl. In a still further aspect, R^{20}, when present, is isopropyl. In yet a further aspect, R^{20}, when present, is methyl.

[0262] In a further aspect, R^{20}, when present, is selected from —$CH_2C_6H_5$ and —CH_2Cy^1. In a still further aspect, R^{20}, when present, is —$CH_2C_6H_5$. In yet a further aspect, R^{20}, when present, is —CH_2Cy^1.

[0263] In a further aspect, R^{20}, when present, is selected from hydrogen, —$(CH_2)_3NHC(NH)NH_2$, and —$(CH_2)_4NH_2$. In a still further aspect, R^{20}, when present, is selected from hydrogen and —$(CH_2)_3NHC(NH)NH_2$. In yet a further

aspect, R^{20}, when present, is selected from hydrogen and —$(CH_2)_4NH_2$. In an even further aspect, R^{20}, when present, is —$(CH_2)_3NHC(NH)NH_2$. In a still further aspect, R^{20}, when present, is —$(CH_2)_4NH_2$.

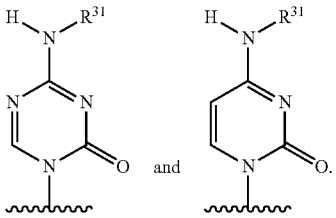
[0264] In a further aspect, R^{20}, when present, is selected from hydrogen, —CH_2CO_2H, —$(CH_2)_2CO_2H$, —$CH_2C(O)NH_2$, and —$(CH_2)_2C(O)NH_2$. In a still further aspect, R^{20}, when present, is selected from hydrogen, —CH_2CO_2H, and —$(CH_2)_2CO_2H$. In yet a further aspect, R^{20}, when present, is selected from hydrogen, —$CH_2C(O)NH_2$, and —$(CH_2)_2C(O)NH_2$. In an even further aspect, R^{20}, when present, is selected from hydrogen and —CH_2CO_2H. In a still further aspect, R^{20}, when present, is selected from hydrogen and —$(CH_2)_2CO_2H$. In yet a further aspect, R^{20}, when present, is selected from hydrogen and —$CH_2C(O)NH_2$. In an even further aspect, R^{20}, when present, is selected from hydrogen and —$(CH_2)_2C(O)NH_2$. In a still further aspect, R^{20}, when present, is CH_2CO_2H. In yet a further aspect, R^{20}, when present, is —$(CH_2)_2CO_2H$. In an even further aspect, R^{20}, when present, is —$CH_2C(O)NH_2$. In a still further aspect, R^{20}, when present, is —$(CH_2)_2C(O)NH_2$.

[0265] In a further aspect, R^{20}, when present, is selected from hydrogen, —CH_2OH, —$CH(OH)CH_3$, —CH_2SH, —$(CH_2)_2SCH_3$, and CH_2SeH. In a still further aspect, R^{20}, when present, is selected from hydrogen, —CH_2OH, and $CH(OH)CH_3$. In yet a further aspect, R^{20}, when present, is selected from hydrogen, —CH_2SH, and —$(CH_2)_2SCH_3$. In an even further aspect, R^{20}, when present, is selected from hydrogen and —CH_2SeH. In a still further aspect, R^{20}, when present, is selected from CH_2OH and $CH(OH)CH_3$. In yet a further aspect, R^{20}, when present, is selected from —CH_2SH and —$(CH_2)_2SCH_3$. In an even further aspect, R^{20}, when present, is —CH_2SeH. In a still further aspect, R^{20}, when present, is —CH_2OH. In yet a further aspect, R^{20}, when present, is —$CH(OH)CH_3$. In an even further aspect, R^{20}, when present, is —CH_2SH. In a still further aspect, R^{20}, when present, is —$(CH_2)_2SCH_3$.

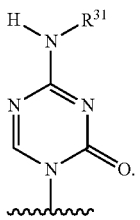
[0266] In a further aspect, R^{20}, when present, is hydrogen.

[0267] m. R^{30} Groups

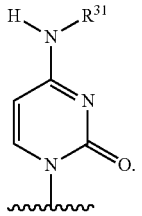
[0268] In one aspect, R^{30}, when present, is a structure selected from:



[0269] In a further aspect, R^{30}, when present, is:



[0270] In a further aspect, R^{30}, when present, is:



[0271] n. R^{31} Groups

[0272] In one aspect, R^{31}, when present, is selected from hydrogen, —C(O)(C1-C30 alkyl), and —C(O)(C2-C30 alkenyl). In a further aspect, R^{31}, when present, is selected from hydrogen, —C(O)(C1-C15 alkyl), and —C(O)(C2-C15 alkenyl). In a still further aspect, R^{31}, when present, is selected from hydrogen, —C(O)(C1-C8 alkyl), and —C(O)(C2-C8 alkenyl). In yet a further aspect, R^{31}, when present, is selected from hydrogen, fluoro, —C(O)(C1-C4 alkyl), and —C(O)(C2-C4 alkenyl). In an even further aspect, R^{31}, when present, is selected from hydrogen, —$C(O)CH_3$, —$C(O)CH_2CH_3$, —$C(O)CH(CH_3)_2$, —$C(O)CH_2CH_2CH_3$, —$C(O)CH{=}CH_2$, —$C(O)C(CH_3){=}CH_2$, —$C(O)CH{=}CHCH_3$, and —$C(O)CH_2CH{=}CH_2$. In a still further aspect, R^{31}, when present, is selected from hydrogen, —$C(O)CH_3$, —$C(O)CH_2CH_3$, —$C(O)CH(CH_3)_2$, —$C(O)CH_2CH_2CH_3$, and —$C(O)CH{=}CH_2$.

[0273] In a further aspect, R^{31}, when present, is selected from hydrogen and —C(O)(C1-C30 alkyl). In a still further aspect, R^{31}, when present, is selected from hydrogen and —C(O)(C1-C15 alkyl). In yet a further aspect, R^{31}, when present, is selected from hydrogen and —C(O)(C1-C8 alkyl). In an even further aspect, R^{31}, when present, is selected from hydrogen and —C(O)(C1-C4 alkyl). In a still further aspect, R^{31}, when present, is selected from hydrogen, —$C(O)CH_3$, —$C(O)CH_2CH_3$, —$C(O)CH(CH_3)_2$, and —$C(O)CH_2CH_2CH_3$. In yet a further aspect, R^{31}, when present, is selected from hydrogen, —$C(O)CH_3$, and —$C(O)CH_2CH_3$. In an even further aspect, R^{31}, when present, is selected from hydrogen and —$C(O)CH_2CH_3$. In a still further aspect, R^{31}, when present, is selected from hydrogen and —$C(O)CH_3$.

[0274] In a further aspect, R^{31}, when present, is selected from hydrogen and —C(O)(C2-C30 alkenyl). In a still further aspect, R^{31}, when present, is selected from hydrogen and —C(O)(C2-C15 alkenyl). In yet a further aspect, R^{31}, when present, is selected from hydrogen and —C(O)(C2-C8 alkenyl). In an even further aspect, R^{31}, when present, is selected from hydrogen and —C(O)(C2-C4 alkenyl). In a still further aspect, R^{31}, when present, is selected from hydrogen, —$C(O)CH{=}CH_2$, —$C(O)C(CH_3){=}CH_2$, —$C(O)CH{=}CHCH_3$, and —$C(O)CH_2CH{=}CH_2$. In yet a further aspect, R^{31}, when present, is selected from hydrogen and —$C(O)CH{=}CH_2$.

[0275] In a further aspect, R^{31}, when present, is selected from —C(O)(C1-C30 alkyl) and —C(O)(C2-C30 alkenyl). In a still further aspect, R^{31}, when present, is selected from —C(O)(C1-C15 alkyl) and —C(O)(C2-C15 alkenyl). In yet a further aspect, R^{31}, when present, is selected from —C(O)(C1-C8 alkyl) and —C(O)(C2-C8 alkenyl). In an even further aspect, R^{31}, when present, is selected from —C(O)(C1-C4 alkyl) and —C(O)(C2-C4 alkenyl). In a still further

aspect, R^{31}, when present, is selected from —C(O)CH_3, —C(O)CH_2CH_3, —C(O)$CH(CH_3)_2$, —C(O)$CH_2CH_2CH_3$, —C(O)CH═CH_2, —C(O)$C(CH_3)$═CH_2, —C(O)CH═$CHCH_3$, and —C(O)CH_2CH═CH_2. In yet a further aspect, R^{31}, when present, is selected from —C(O)CH_3, —C(O)CH_2CH_3, —C(O)$CH(CH_3)_2$, and —C(O)CH═CH_2.

[0276] In a further aspect, R^{31}, when present, is —C(O)(C1-C30 alkyl). In a still further aspect, R^{31}, when present, is —C(O)(C1-C15 alkyl). In yet a further aspect, R^{31}, when present, is —C(O)(C1-C8 alkyl). In an even further aspect, R^{31}, when present, is —C(O)(C1-C4 alkyl). In a still further aspect, R^{31}, when present, is selected from —C(O)CH_3, —C(O)CH_2CH_3, —C(O)$CH(CH_3)_2$, and —C(O)$CH_2CH_2CH_3$. In yet a further aspect, R^{31}, when present, is selected from —C(O)CH_3 and —C(O)CH_2CH_3. In an even further aspect, R^{31}, when present, is —C(O)CH_2CH_3. In a still further aspect, R^{31}, when present, is —C(O)CH_3.

[0277] In a further aspect, R^{31}, when present, is —C(O)(C2-C30 alkenyl). In a still further aspect, R^{31}, when present, is —C(O)(C2-C15 alkenyl). In yet a further aspect, R^{31}, when present, is —C(O)(C2-C8 alkenyl). In an even further aspect, R^{31}, when present, is —C(O)(C2-C4 alkenyl). In a still further aspect, R^{31}, when present, is selected from —C(O)CH═CH_2, —C(O)$C(CH_3)$═CH_2, —C(O)CH═$CHCH_3$, and —C(O)CH_2CH═CH_2. In yet a further aspect, R^{31}, when present, is —C(O)CH═CH_2.

[0278] In a further aspect, R^{31}, when present, is hydrogen.

[0279] o. Cy^1 Groups

[0280] In one aspect, Cy^1, when present, is selected from monocylic aryl, para-hydroxy monocyclic aryl, 4-imidazolyl, and 3-indolyl. In a further aspect, Cy^1, when present, is selected from monocylic aryl and para-hydroxy monocyclic aryl. In a still further aspect, Cy^1, when present, is selected from 4-imidazolyl and 3-indolyl. In yet a further aspect, Cy^1, when present, is selected from monocylic aryl and 4-imidazolyl. In an even further aspect, Cy^1, when present, is selected from para-hydroxy monocyclic aryl and 3-indolyl.

[0281] In a further aspect, Cy^1, when present, is monocylic aryl. In a still further aspect, Cy^1, when present, is para-hydroxy monocyclic aryl.

[0282] In a further aspect, Cy^1, when present, is 4-imidazolyl. In a still further aspect, Cy^1, when present, is 3-indolyl.

[0283] p. Ar^1 Groups

[0284] In one aspect, Ar^1, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a further aspect, Ar^1, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, or 2 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^1, when present, is selected from aryl and heteroaryl and is substituted with 0 or 1 group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In yet a further aspect, Ar^1, when present, is selected from aryl and heteroaryl and is monosubstituted with a group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In an even further aspect, Ar^1, when present, is selected from aryl and heteroaryl and is unsubstituted.

[0285] In a further aspect, Ar^1, when present, is aryl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^1, when present, is aryl substituted with 0, 1, or 2 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In yet a further aspect, Ar^1, when present, is aryl substituted with 0 or 1 group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In an even further aspect, Ar^1, when present, is aryl monosubstituted with a group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^1, when present, is unsubstituted aryl.

[0286] In a further aspect, Ar^1, when present, is phenyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^1, when present, is phenyl substituted with 0, 1, or 2 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In yet a further aspect, Ar^1, when present, is phenyl substituted with 0 or 1 group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In an even further aspect, Ar^1, when present, is phenyl monosubstituted with a group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^1, when present, is unsubstituted phenyl.

[0287] In a further aspect, Ar^1, when present, is naphthyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^1, when present, is naphthyl substituted with 0, 1, or 2 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In yet a further aspect, Ar^1, when present, is naphthyl substituted with 0 or 1 group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In an even further aspect, Ar^1, when present, is naphthyl monosubstituted with a group selected from halo-

gen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^1, when present, is unsubstituted naphthyl.

[0288] In a further aspect, Ar^1, when present, is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^1, when present, is heteroaryl substituted with 0, 1, or 2 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In yet a further aspect, Ar^1, when present, is heteroaryl substituted with 0 or 1 group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In an even further aspect, Ar^1, when present, is heteroaryl monosubstituted with a group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^1, when present, is unsubstituted heteroaryl.

[0289] In a further aspect, Ar^1, when present, is pyridinyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^1, when present, is pyridinyl substituted with 0, 1, or 2 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In yet a further aspect, Ar^1, when present, is pyridinyl substituted with 0 or 1 group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In an even further aspect, Ar^1, when present, is pyridinyl monosubstituted with a group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^1, when present, is unsubstituted pyridinyl.

[0290] q. Ar^2 Groups

[0291] In one aspect, Ar^2, when present, is selected from aryl and heteroaryl substituted with 1 or 2 groups independently selected from C1-C10 alkyl and nitro. In a further aspect, Ar^2, when present, is selected from aryl and heteroaryl substituted with 2 groups independently selected from C1-C10 alkyl and nitro. In a still further aspect, Ar^2, when present, is selected from aryl and heteroaryl substituted with 1 group selected from C1-C10 alkyl and nitro.

[0292] In a further aspect, Ar^2, when present, is aryl substituted with 1 or 2 groups independently selected from C1-C10 alkyl and nitro. In a still further aspect, Ar^2, when present, is aryl substituted with 2 groups independently selected from C1-C10 alkyl and nitro. In yet a further aspect, Ar^2, when present, is aryl substituted with 1 group selected from C1-C10 alkyl and nitro.

[0293] In a further aspect, Ar^2, when present, is phenyl substituted with 1 or 2 groups independently selected from C1-C10 alkyl and nitro. In a still further aspect, Ar^2, when present, is phenyl substituted with 2 groups independently selected from C1-C10 alkyl and nitro. In yet a further aspect, Ar^2, when present, is phenyl substituted with 1 group selected from C1-C10 alkyl and nitro.

[0294] In a further aspect, Ar^2, when present, is naphthyl substituted with 1 or 2 groups independently selected from C1-C10 alkyl and nitro. In a still further aspect, Ar^2, when present, is naphthyl substituted with 2 groups independently selected from C1-C10 alkyl and nitro. In yet a further aspect, Ar^2, when present, is naphthyl substituted with 1 group selected from C1-C10 alkyl and nitro.

[0295] In a further aspect, Ar^2, when present, is heteroaryl substituted with 1 or 2 groups independently selected from C1-C10 alkyl and nitro. In a still further aspect, Ar^2, when present, is heteroaryl substituted with 2 groups independently selected from C1-C10 alkyl and nitro. In yet a further aspect, Ar^2, when present, is heteroaryl substituted with 1 group selected from C1-C10 alkyl and nitro.

[0296] In a further aspect, Ar^2, when present, is pyridinyl substituted with 1 or 2 groups independently selected from C1-C10 alkyl and nitro. In a still further aspect, Ar^2, when present, is pyridinyl substituted with 2 groups independently selected from C1-C10 alkyl and nitro. In yet a further aspect, Ar^2, when present, is pyridinyl substituted with 1 group selected from C1-C10 alkyl and nitro.

[0297] r. Ar^3 Groups

[0298] In one aspect, Ar^3, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a further aspect, Ar^3, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, or 2 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^3, when present, is selected from aryl and heteroaryl and is substituted with 0 or 1 group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In yet a further aspect, Ar^3, when present, is selected from aryl and heteroaryl and is monosubstituted with a group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In an even further aspect, Ar^3, when present, is selected from aryl and heteroaryl and is unsubstituted.

[0299] In a further aspect, Ar^3, when present, is aryl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^3, when present, is aryl substituted with 0, 1, or 2 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4

aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In yet a further aspect, Ar^3, when present, is aryl substituted with 0 or 1 group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In an even further aspect, Ar^3, when present, is aryl monosubstituted with a group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^3, when present, is unsubstituted aryl.

[0300] In a further aspect, Ar^3, when present, is phenyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^3, when present, is phenyl substituted with 0, 1, or 2 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In yet a further aspect, Ar^3, when present, is phenyl substituted with 0 or 1 group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In an even further aspect, Ar^3, when present, is phenyl monosubstituted with a group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^3, when present, is unsubstituted phenyl.

[0301] In a further aspect, Ar^3, when present, is naphthyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^3, when present, is naphthyl substituted with 0, 1, or 2 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In yet a further aspect, Ar^3, when present, is naphthyl substituted with 0 or 1 group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In an even further aspect, Ar^3, when present, is naphthyl monosubstituted with a group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^3, when present, is unsubstituted naphthyl.

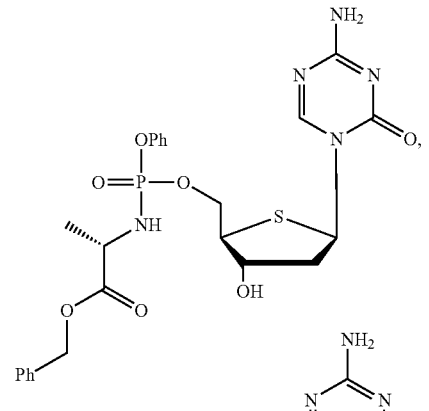
[0302] In a further aspect, Ar^3, when present, is heteroaryl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^3, when present, is heteroaryl substituted with 0, 1, or 2 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In yet a further aspect, Ar^3, when present, is heteroaryl substituted with 0 or 1 group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In an even further aspect, Ar^3, when present, is heteroaryl monosubstituted with a group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^3, when present, is unsubstituted heteroaryl.

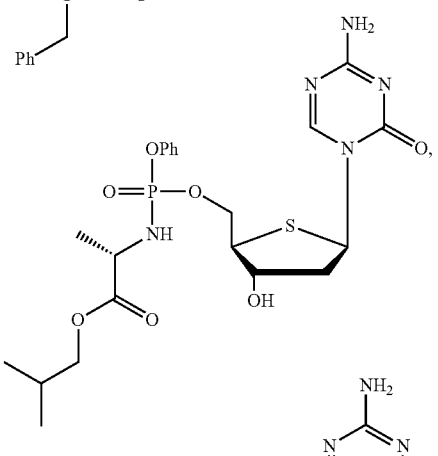
[0303] In a further aspect, Ar^3, when present, is pyridinyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^3, when present, is pyridinyl substituted with 0, 1, or 2 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In yet a further aspect, Ar^3, when present, is pyridinyl substituted with 0 or 1 group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In an even further aspect, Ar^3, when present, is pyridinyl monosubstituted with a group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^3, when present, is unsubstituted pyridinyl.

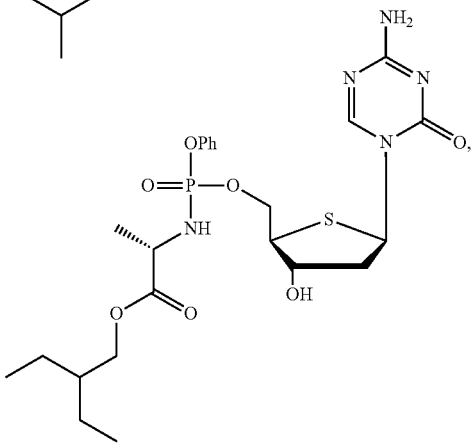
[0304] In a further aspect, Ar^3, when present, is furanyl substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^3, when present, is furanyl substituted with 0, 1, or 2 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In yet a further aspect, Ar^3, when present, is furanyl substituted with 0 or 1 group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In an even further aspect, Ar^3, when present, is furanyl monosubstituted with a group selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C10 alkylamino, and (C1-C4)(C1-C4) dialkylamino. In a still further aspect, Ar^3, when present, is unsubstituted furanyl.

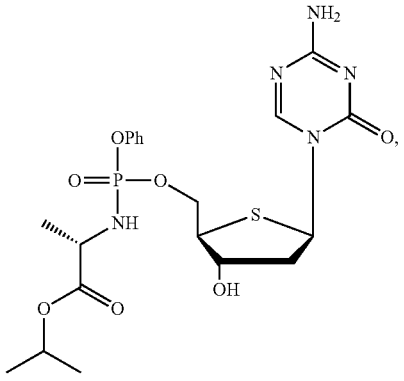
[0305] 2. Example Compounds

[0306] In one aspect, a compound can be present as one or more of the following structures:









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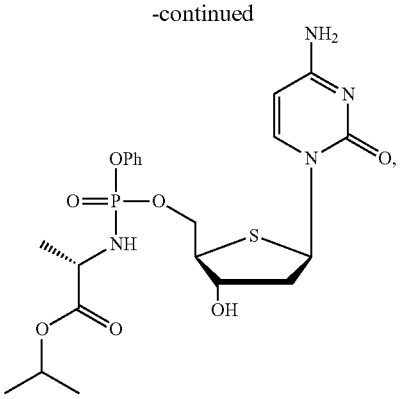

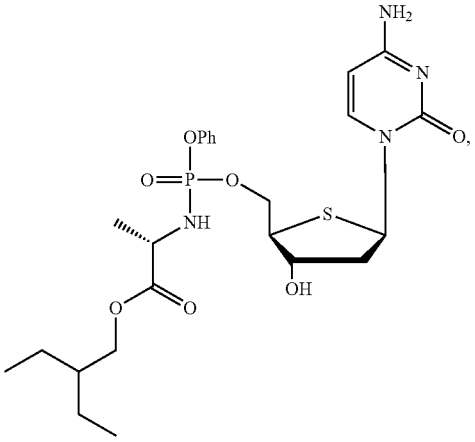

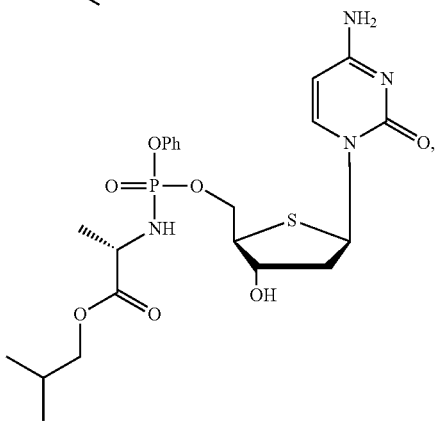

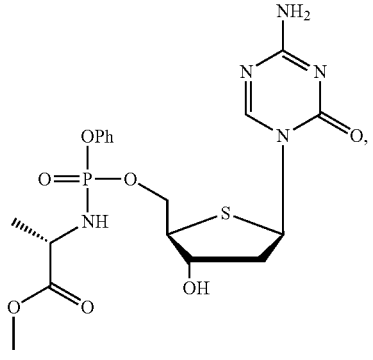

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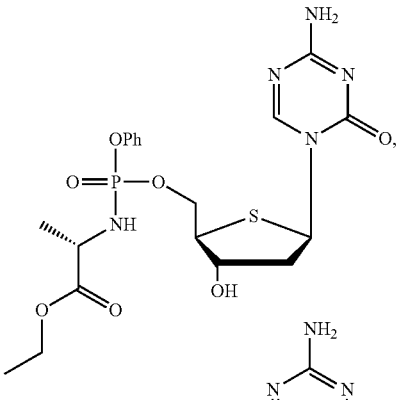

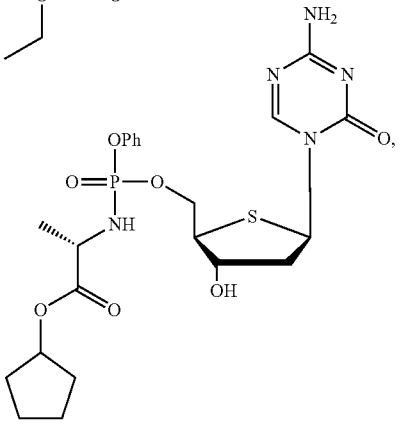

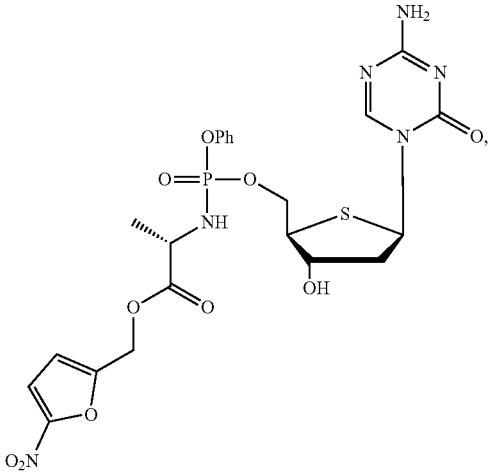

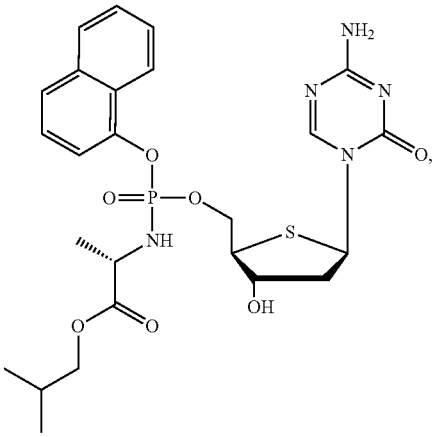

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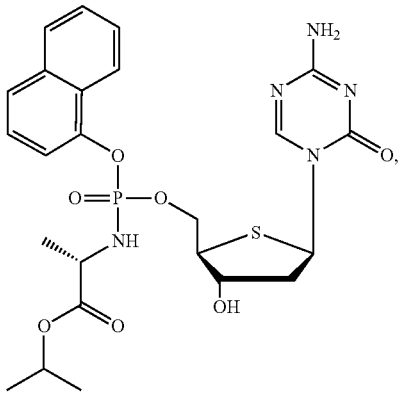

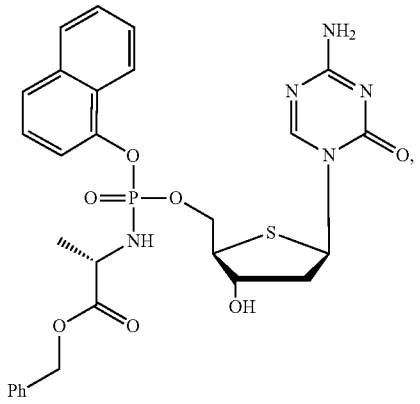

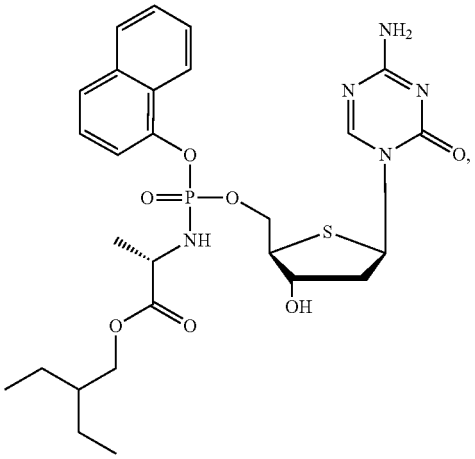

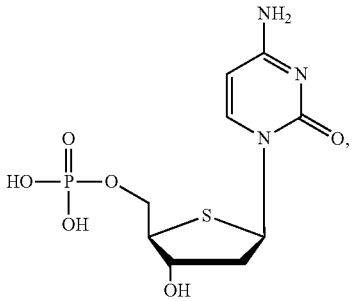

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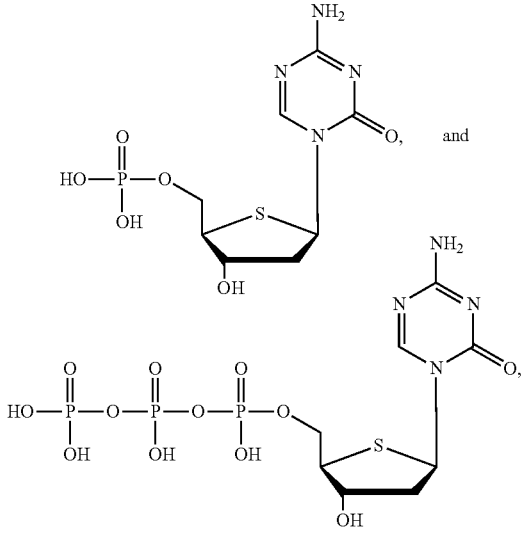


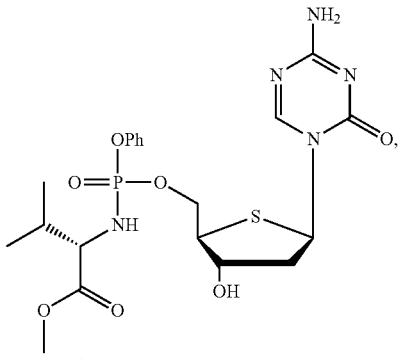
and

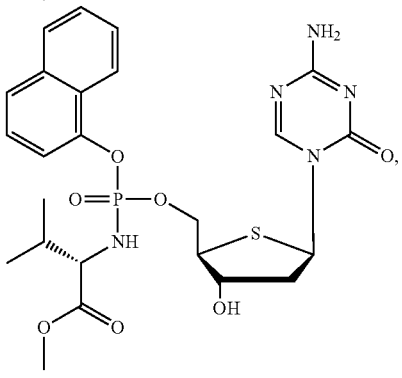
or a pharmaceutically acceptable salt thereof.

[0307] 3. Prophetic Compound Examples

[0308] The following compound examples are prophetic, and can be prepared using the synthesis methods described herein above and other general methods as needed as would be known to one skilled in the art. It is anticipated that the prophetic compounds would be useful for the treatment of disorders of uncontrolled cellular proliferation such as, for example, cancer, and such utility can be determined using the assay methods described herein below.

[0309] In one aspect, a compound can be selected from:





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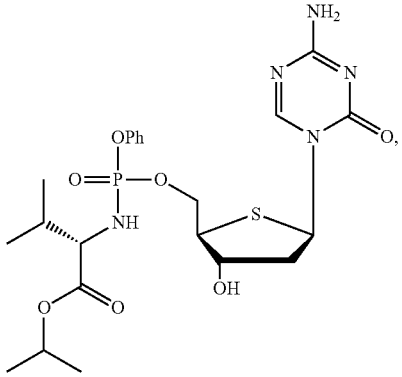

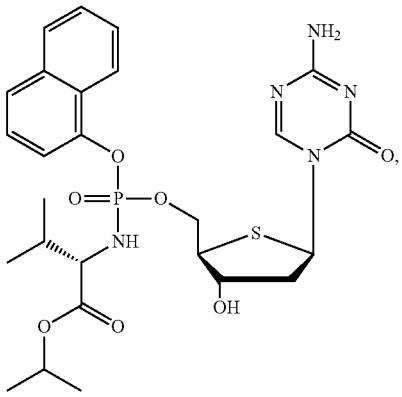

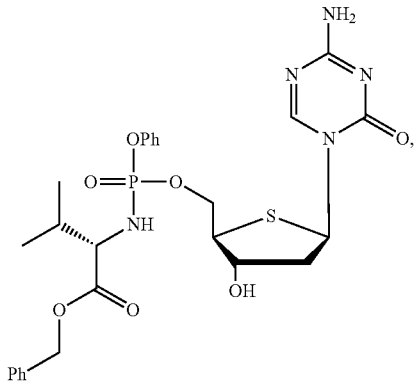

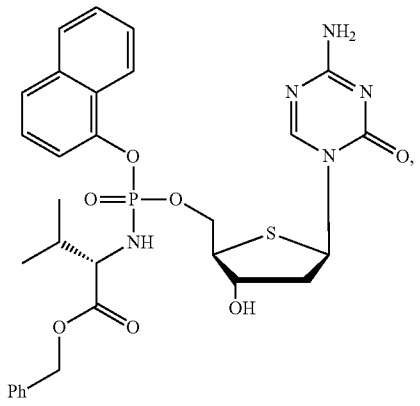

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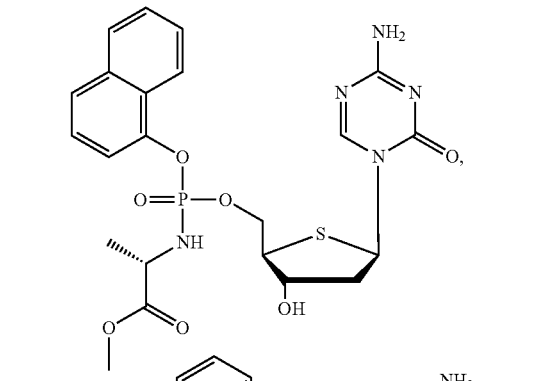

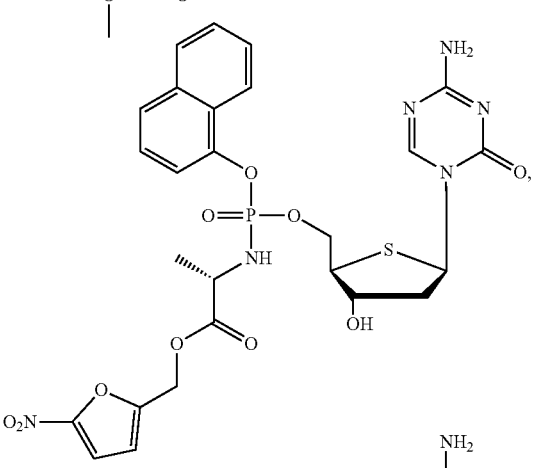

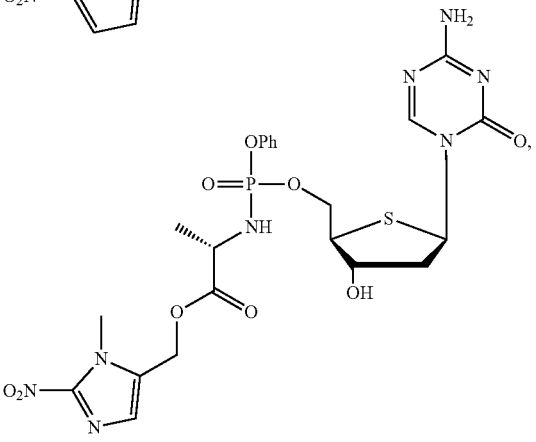

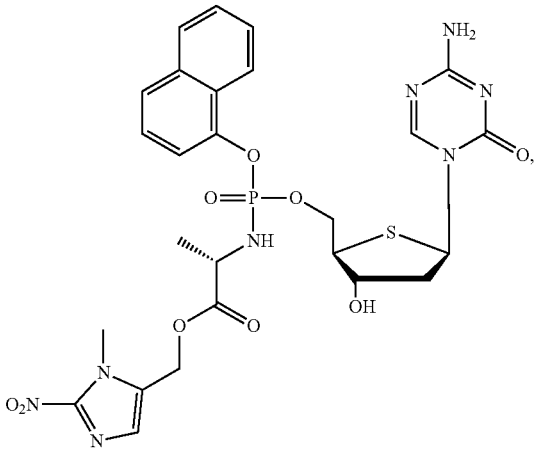

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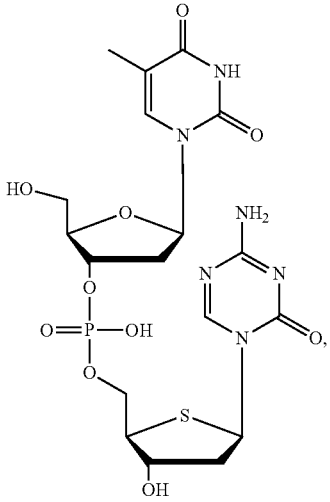

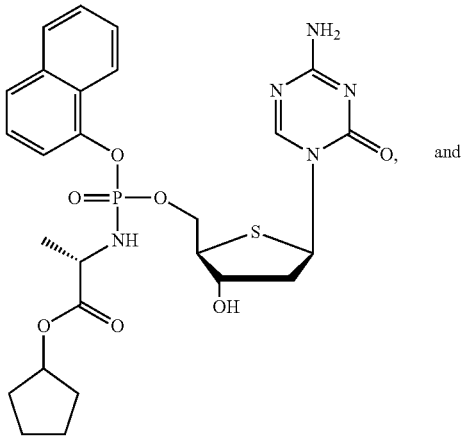

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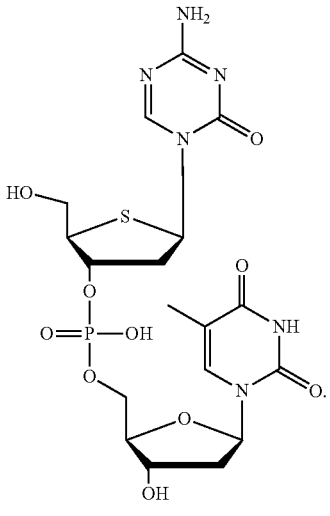
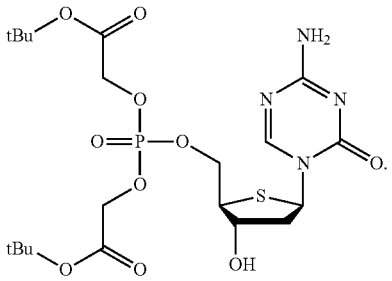


[0310] In one aspect, a compound can be:



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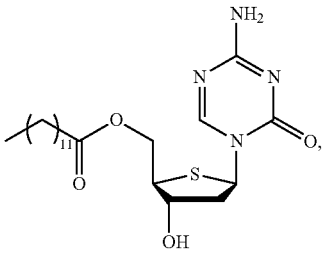

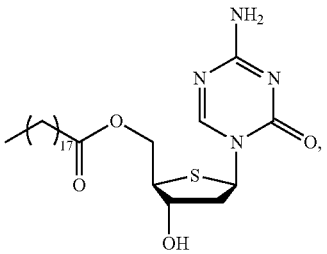

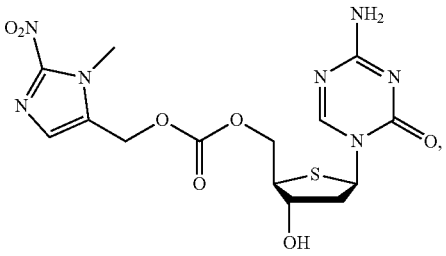

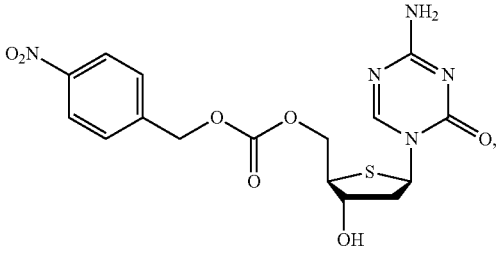

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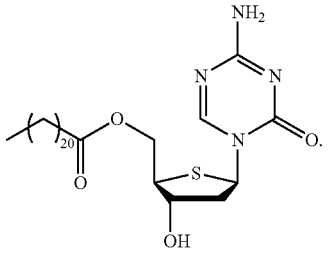

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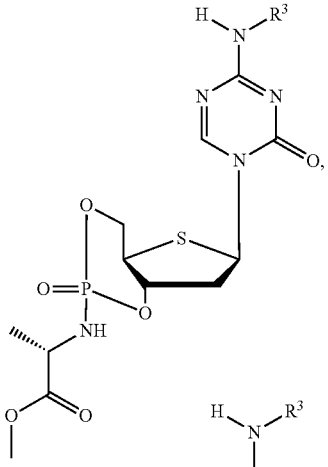

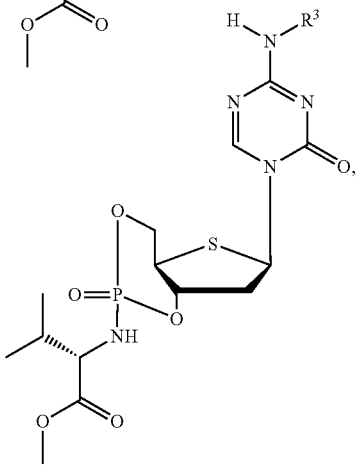

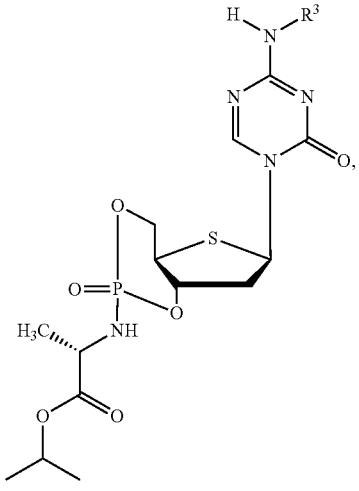

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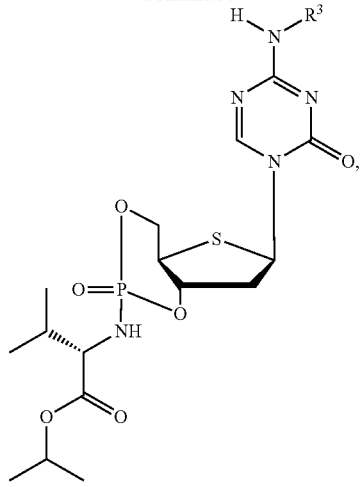

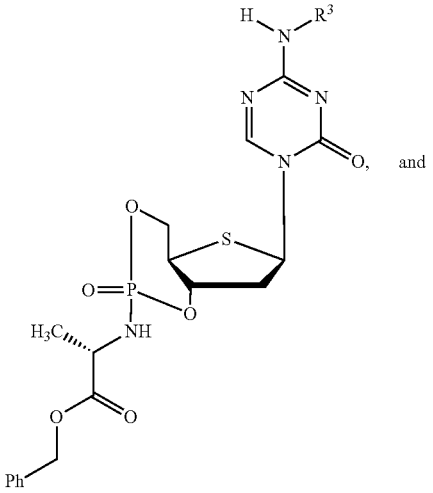

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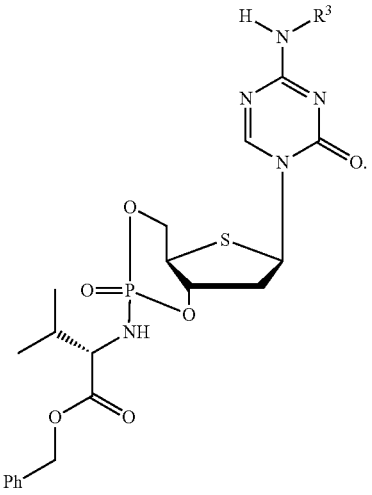

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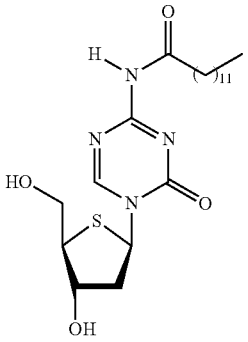

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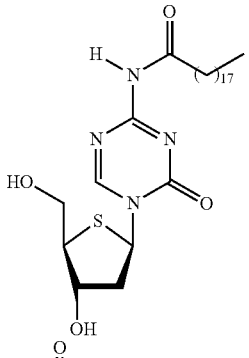

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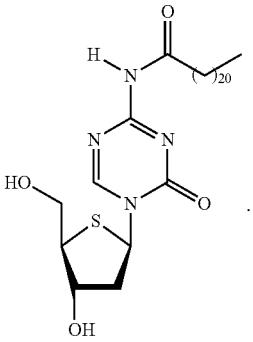

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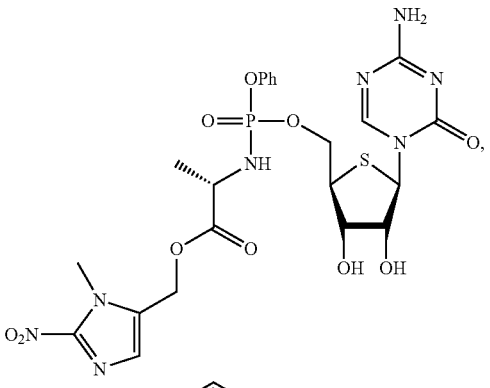
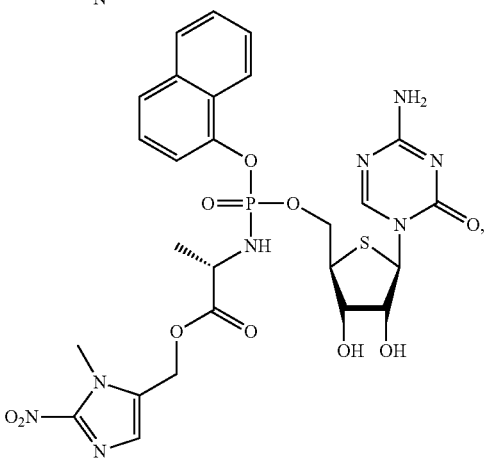
[0314] In one aspect, a compound can be selected from:





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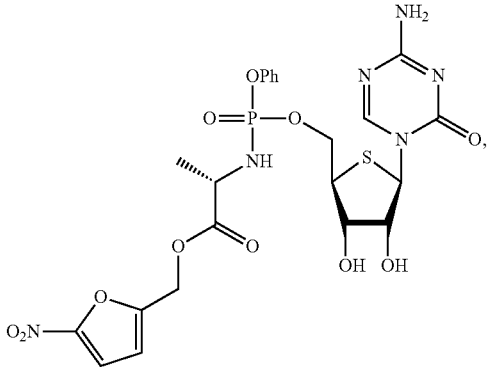

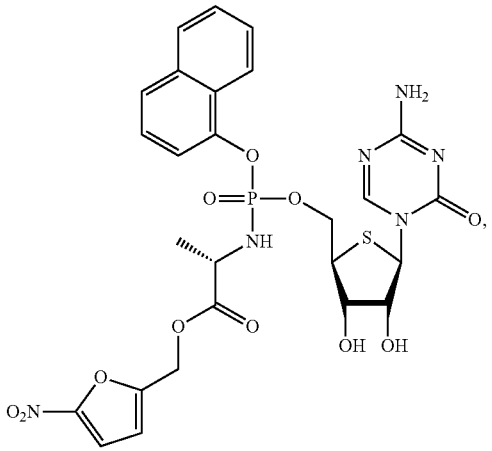

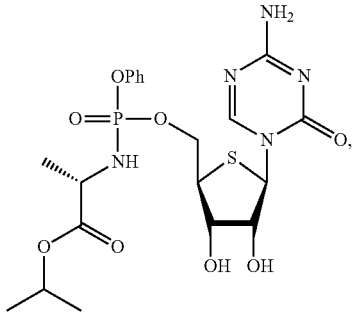

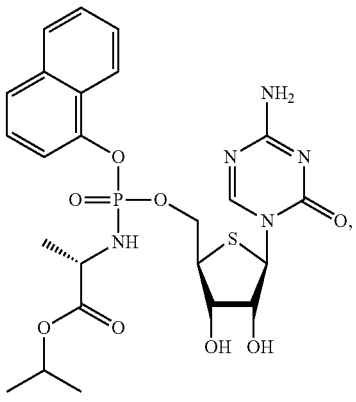

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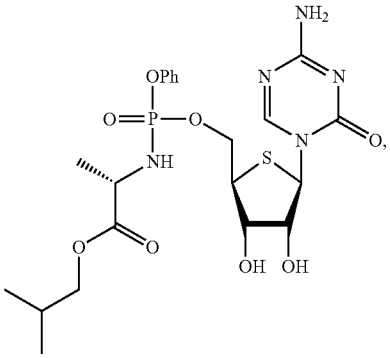

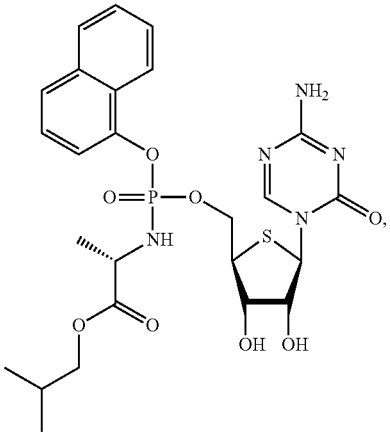

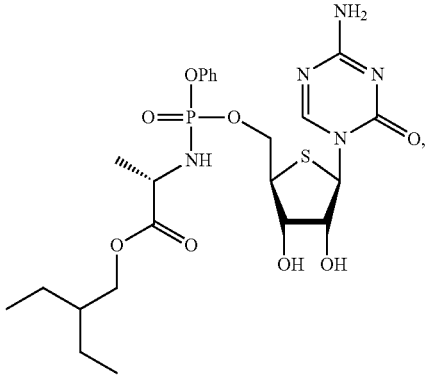

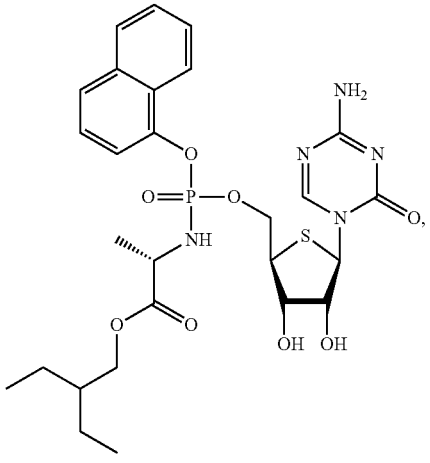

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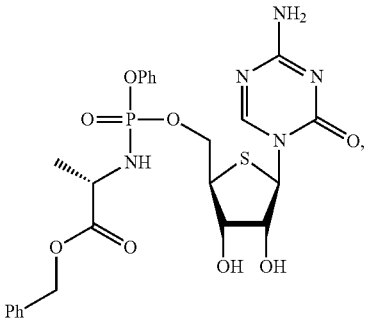

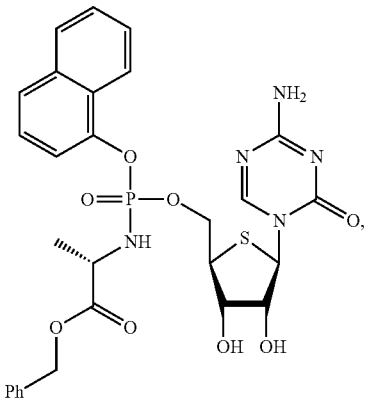

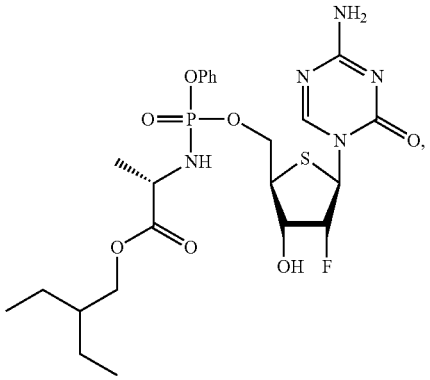

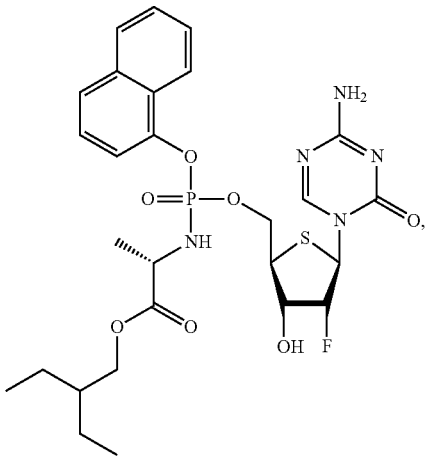

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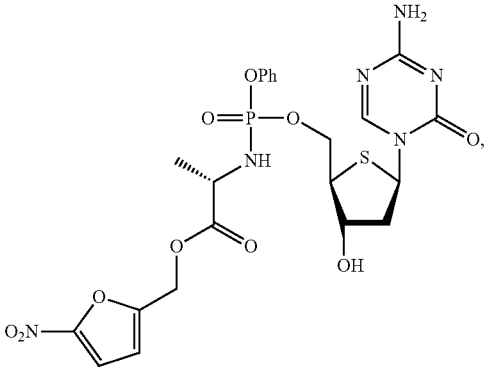

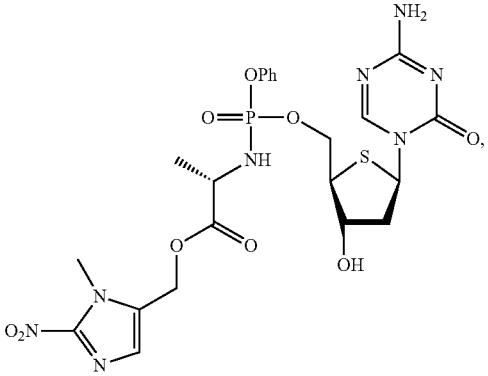

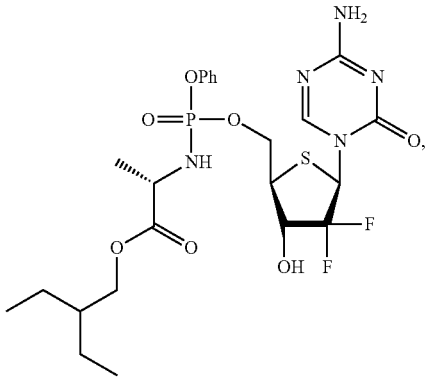

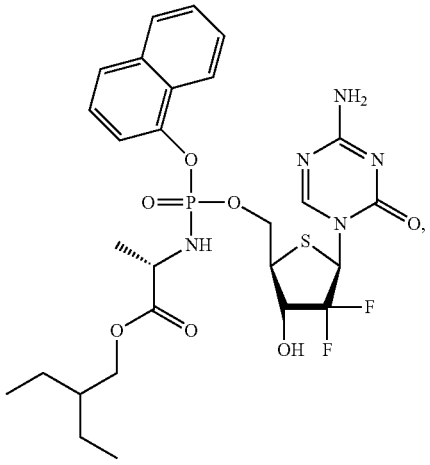

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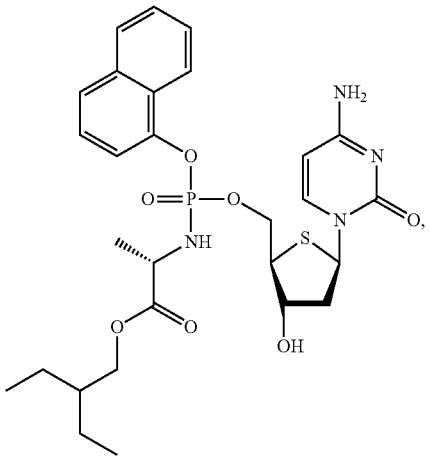

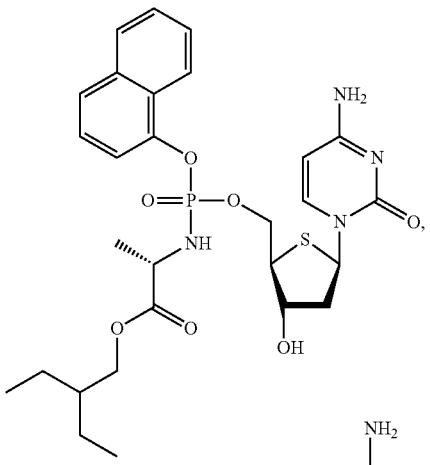

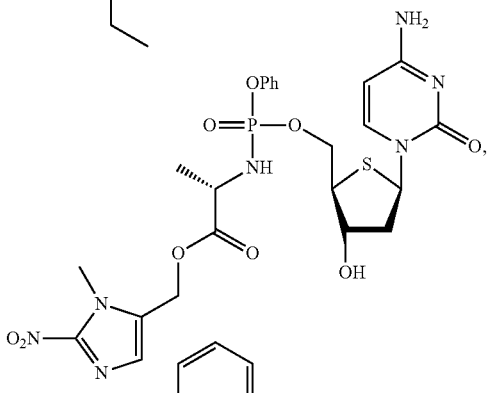

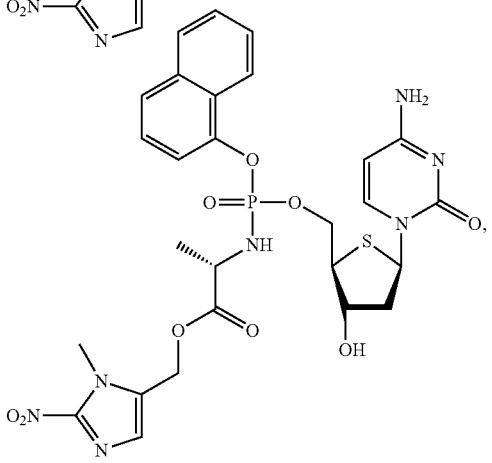

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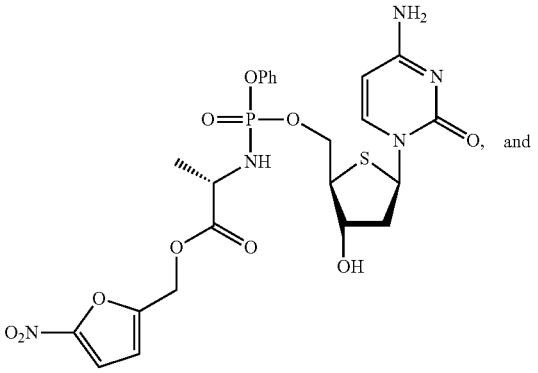
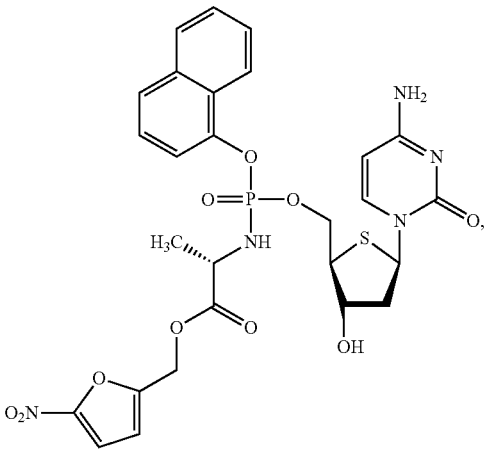
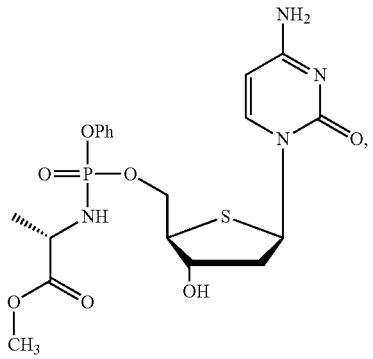
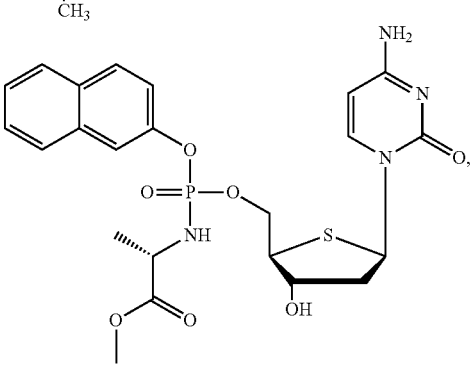


and



[0315] In one aspect, a compound can be selected from:





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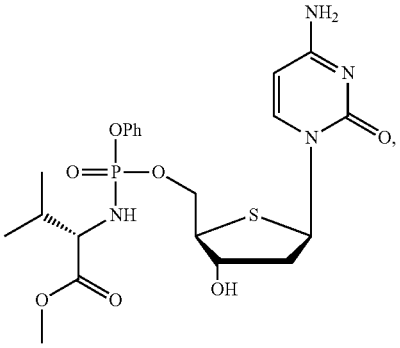

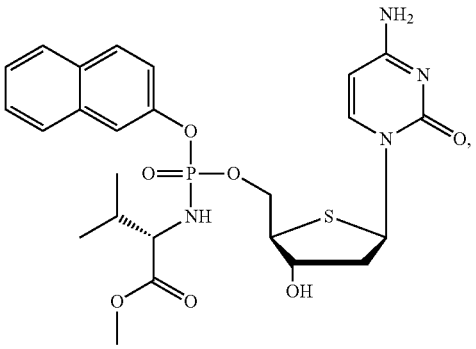

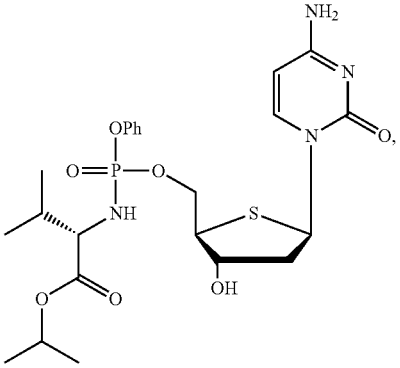

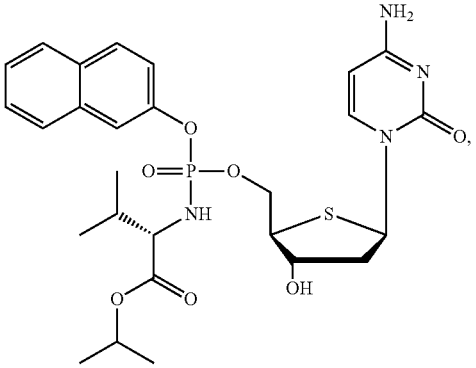

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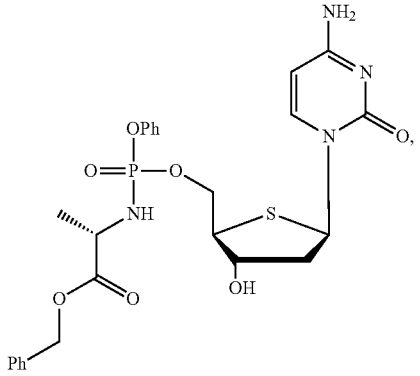

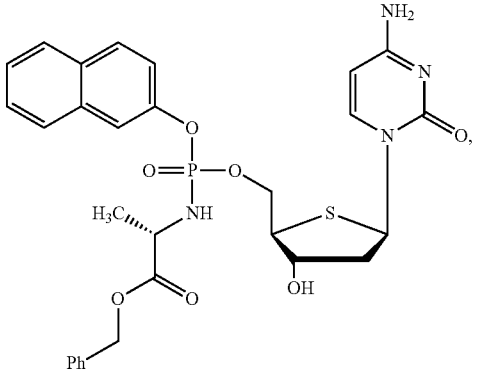

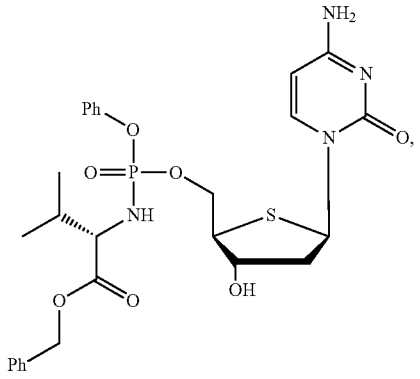

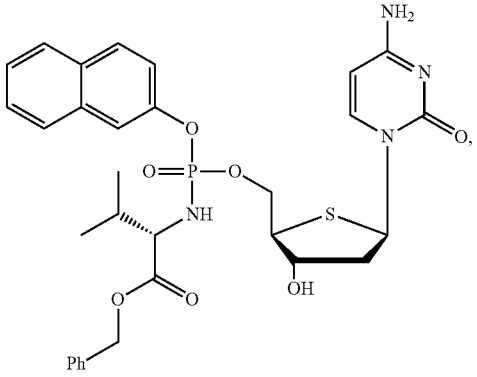

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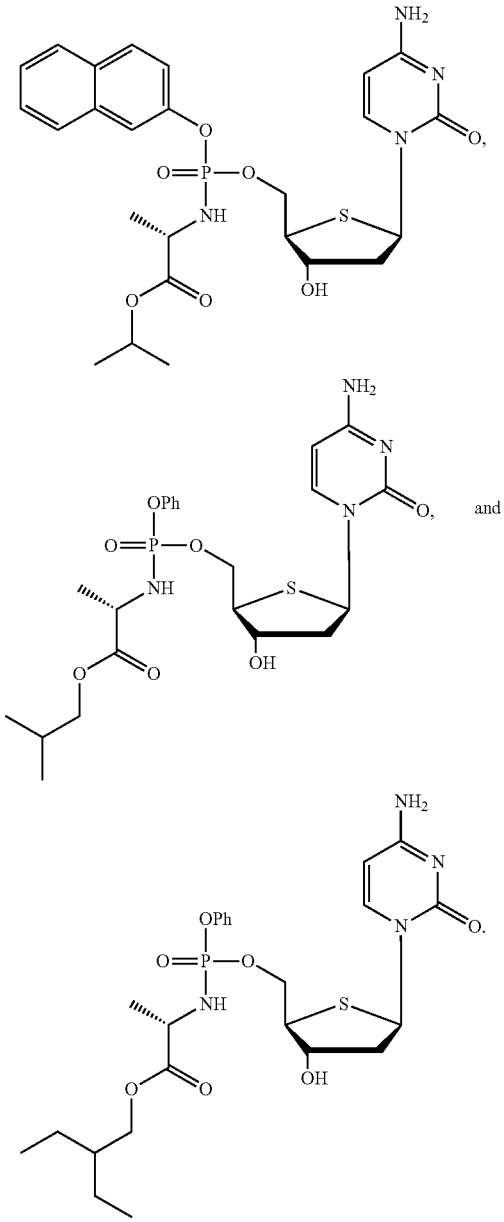
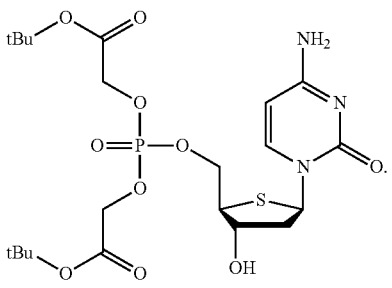
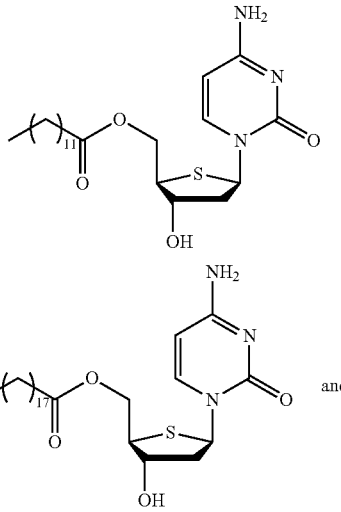


and

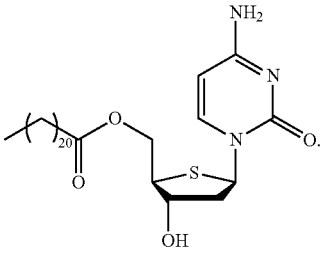
[0316] In one aspect, a compound can be:



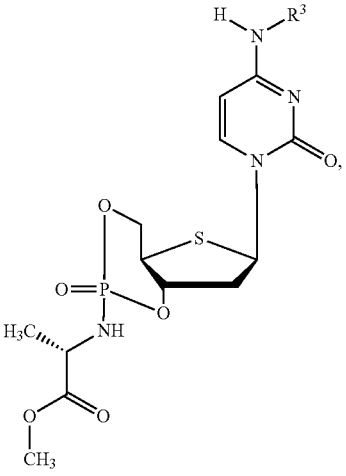
[0317] In one aspect, a compound can be selected from:



and



[0318] In one aspect, a compound can be selected from:



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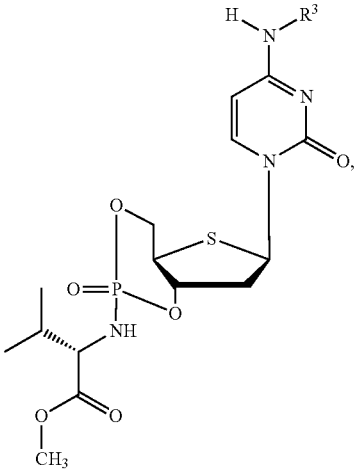

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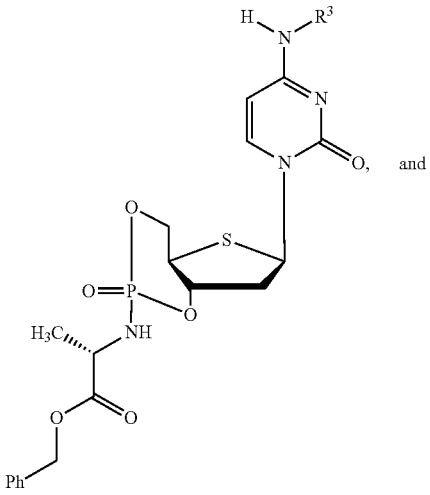
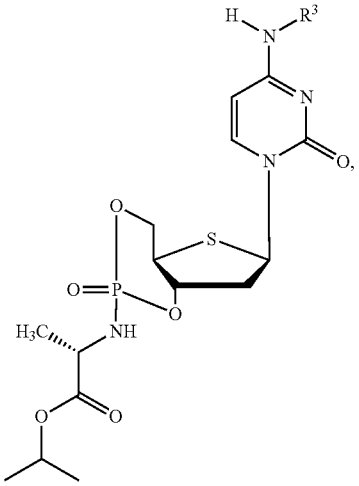
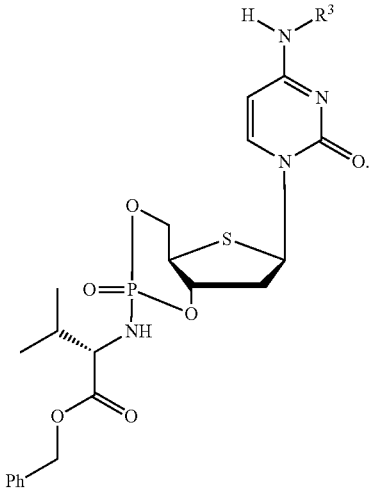
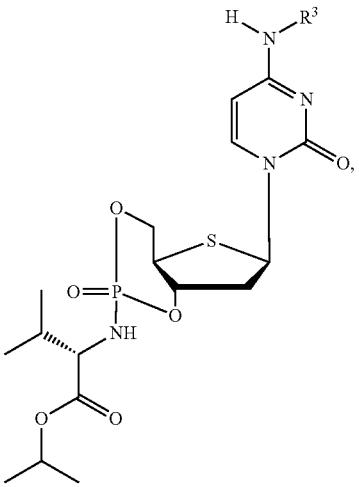


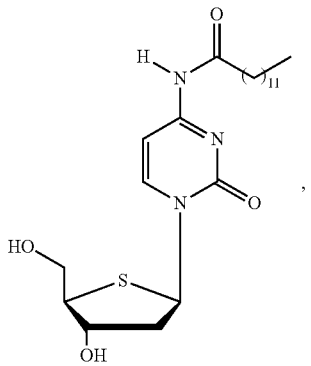
and







[0319] In one aspect, a compound can be selected from:



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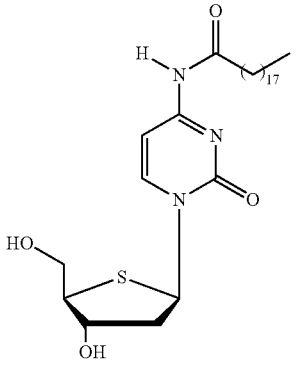
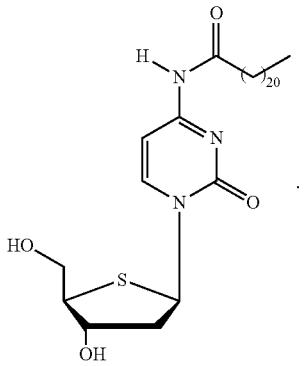


, and



.

[0320] It is contemplated that one or more compounds can optionally be omitted from the disclosed invention.

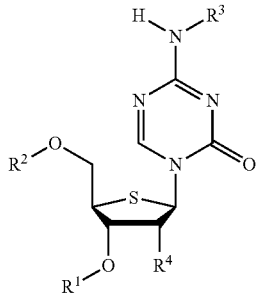
[0321] It is understood that the disclosed compounds can be used in connection with the disclosed methods, compositions, kits, and uses.

[0322] It is understood that pharmaceutical acceptable derivatives of the disclosed compounds can be used also in connection with the disclosed methods, compositions, kits, and uses. The pharmaceutical acceptable derivatives of the compounds can include any suitable derivative, such as pharmaceutically acceptable salts as discussed below, isomers, radiolabeled analogs, tautomers, and the like.

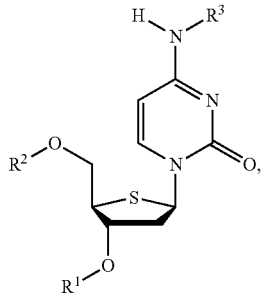
C. Pharmaceutical Compositions

[0323] In one aspect, disclosed are pharmaceutical compositions comprising a disclosed compound, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

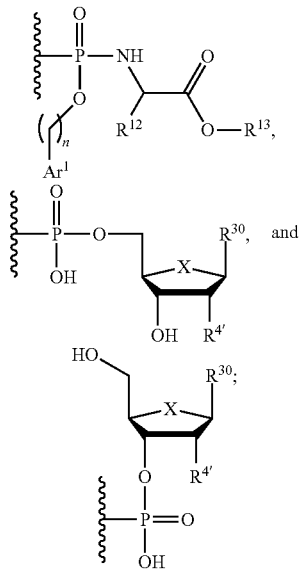
[0324] In one aspect, disclosed are pharmaceutical compositions comprising an effective amount of at least one compound having a structure represented by a formula selected from:



and

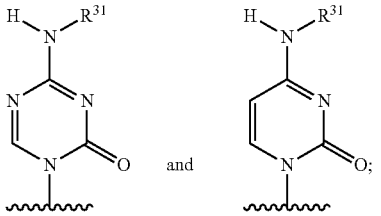


wherein each of R^1 and R^2 is independently selected from hydrogen, —C(O)R^{10}, —P(O)(OR^{11})$_2$, —P(O)(OH)OP(O)(OH)OP(O)(OH)$_2$, and a structure represented by a formula selected from:

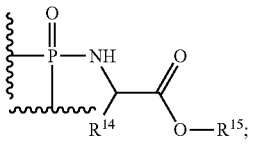


provided that one of R^1 and R^2 is hydrogen; wherein n is selected from 0, 1, and 2; wherein X, when present, is selected from O and S; wherein R^{10}, when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and —CH(NH_2)R^{20}; wherein R^{20}, when present, is selected from hydrogen, methyl, isopropyl, isobutyl, sec-butyl, —$(CH_2)_3NHC(NH)NH_2$, —$(CH_2)_4NH_2$, —CH_2CO_2H, —$(CH_2)_2CO_2H$, —CH_2OH, —$CH(OH)CH_3$, —$CH_2C(O)NH_2$, —$(CH_2)_2C(O)NH_2$, —CH_2SH, —$(CH_2)_2SCH_3$, —CH_2SeH, —$CH_2C_6H_5$, and —CH_2Cy^1; wherein Cy^1, when present, is selected from monocylic aryl, para-hydroxy monocyclic aryl, 4-imidazolyl, and 3-indolyl; wherein each occurrence of R^{11}, when present, is independently selected from hydrogen, -(C1-C10 alkyl)CO_2(C1-C10 alkyl), —(C1-C10 alkoxy)CO_2(C1-C10 alkyl), —(C1-C10 alkyl)CO_2(C1-C10 alkylthio), —(C1-C10 alkyl)-S—S—(C1-C10 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH; wherein Ar^2, when present, is selected from aryl and heteroaryl substituted with 1 or 2 groups independently selected from C1-C10 alkyl and nitro; wherein R^{12}, when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl,

C1-C8 alkylamino, —(C1-C8)C(O)NH_2, aryl, and —(CH_2)aryl; wherein R^{13}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar^3; wherein Ar^3, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino; wherein Ar^1, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino; wherein R^{30}, when present, is a structure selected from:



wherein R^{31}, when present, is selected from hydrogen, —C(O)(C1-C30 alkyl), and —C(O)(C2-C30 alkenyl); or wherein each of R^1 and R^2 together comprise a structure represented by a formula:



wherein R^{14}, when present, is C1-C8 alkyl; wherein R^{15}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and aryl substituted with 0 or 1 C1-C10 alkyl groups; wherein R^3 is selected from hydrogen, —C(O)(C1-C30 alkyl), and —C(O)(C2-C30 alkenyl); wherein each of R^4 and $R^{4'}$, when present, is independently selected from hydrogen, fluoro, —CN, C2-C4 alkenyl, C2-C4 alkynyl, C1-C4 haloalkyl, and —OR^{16}; and wherein R^{16}, when present, is selected from hydrogen, methyl, and —C(O)R^{10}, provided that R^1, R^2, and R^3 are not simultaneously hydrogen, or a pharmaceutically acceptable salt thereof.

[0325] In various aspects, the compounds and compositions of the invention can be administered in pharmaceutical compositions, which are formulated according to the intended method of administration. The compounds and compositions described herein can be formulated in a conventional manner using one or more physiologically acceptable carriers or excipients. For example, a pharmaceutical composition can be formulated for local or systemic administration, e.g., administration by drops or injection into the ear, insufflation (such as into the ear), intravenous, topical, or oral administration.

[0326] The nature of the pharmaceutical compositions for administration is dependent on the mode of administration and can readily be determined by one of ordinary skill in the art. In various aspects, the pharmaceutical composition is sterile or sterilizable. The therapeutic compositions featured in the invention can contain carriers or excipients, many of which are known to skilled artisans. Excipients that can be used include buffers (for example, citrate buffer, phosphate buffer, acetate buffer, and bicarbonate buffer), amino acids, urea, alcohols, ascorbic acid, phospholipids, polypeptides (for example, serum albumin), EDTA, sodium chloride, liposomes, mannitol, sorbitol, water, and glycerol. The nucleic acids, polypeptides, small molecules, and other modulatory compounds featured in the invention can be administered by any standard route of administration. For example, administration can be parenteral, intravenous, subcutaneous, or oral. A modulatory compound can be formulated in various ways, according to the corresponding route of administration. For example, liquid solutions can be made for administration by drops into the ear, for injection, or for ingestion; gels or powders can be made for ingestion or topical application. Methods for making such formulations are well known and can be found in, for example, Remington's Pharmaceutical Sciences, 18th Ed., Gennaro, ed., Mack Publishing Co., Easton, Pa. 1990.

[0327] In various aspects, the disclosed pharmaceutical compositions comprise the disclosed compounds (including pharmaceutically acceptable salt(s) thereof) as an active ingredient, a pharmaceutically acceptable carrier, and, optionally, other therapeutic ingredients or adjuvants. The instant compositions include those suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[0328] In various aspects, the pharmaceutical compositions of this invention can include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of the compounds of the invention. The compounds of the invention, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

[0329] The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

[0330] In preparing the compositions for oral dosage form, any convenient pharmaceutical media can be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like can be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid

pharmaceutical carriers are employed. Optionally, tablets can be coated by standard aqueous or nonaqueous techniques.

[0331] A tablet containing the composition of this invention can be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets can be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent.

[0332] The pharmaceutical compositions of the present invention comprise a compound of the invention (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier, and optionally one or more additional therapeutic agents or adjuvants. The instant compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[0333] Pharmaceutical compositions of the present invention suitable for parenteral administration can be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

[0334] Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

[0335] Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, mouth washes, gargles, and the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations can be prepared, utilizing a compound of the invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt % to about 10 wt % of the compound, to produce a cream or ointment having a desired consistency.

[0336] Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories can be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

[0337] In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above can include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of the invention, and/or pharmaceutically acceptable salts thereof, can also be prepared in powder or liquid concentrate form.

[0338] In a further aspect, an effective amount is a therapeutically effective amount. In a still further aspect, an effective amount is a prophylactically effective amount.

[0339] In a further aspect, the pharmaceutical composition is administered to a mammal. In a still further aspect, the mammal is a human. In an even further aspect, the human is a patient.

[0340] In a further aspect, the pharmaceutical composition is used to treat a disorder of uncontrolled cellular proliferation such as, for example, cancers including, but not limited to, sarcomas, carcinomas, hematological cancers, solid tumors, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanomas, gliomas, leukemias, lymphomas, chronic myeloproliferative disorders, myelodysplastic syndromes, myeloproliferative neoplasms, and plasma cell neoplasms (myelomas).

[0341] It is understood that the disclosed compositions can be prepared from the disclosed compounds. It is also understood that the disclosed compositions can be employed in the disclosed methods of using.

D. Methods of Making a Compound

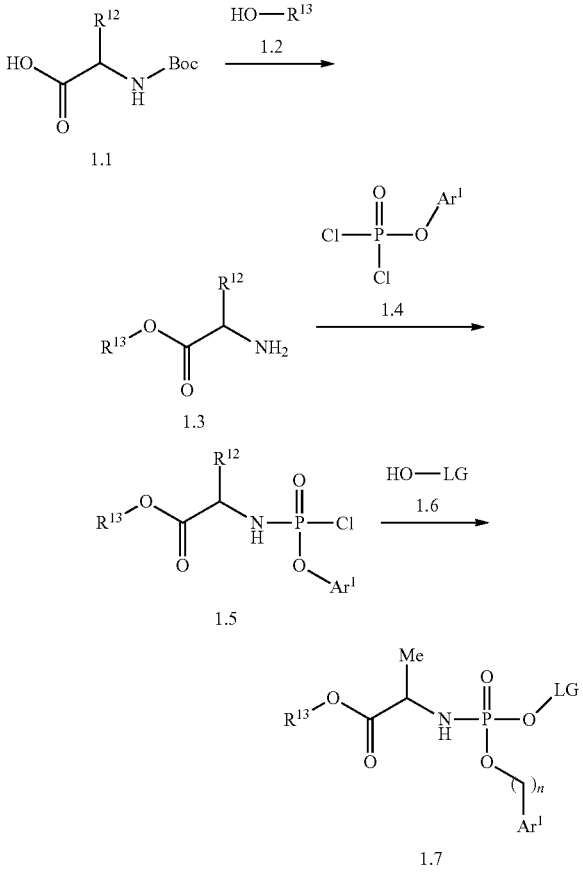
[0342] The compounds of this invention can be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature, exemplified in the experimental sections or clear to one skilled in the art. For clarity, examples having a single substituent are shown where multiple substituents are allowed under the definitions disclosed herein.

[0343] Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the following Reaction Schemes, as described and exemplified below. In certain specific examples, the disclosed compounds can be prepared by Routes I-VIII, as described and exemplified below. The following examples are provided so that the invention might be more fully understood, are illustrative only, and should not be construed as limiting.

[0344] 1. Route I

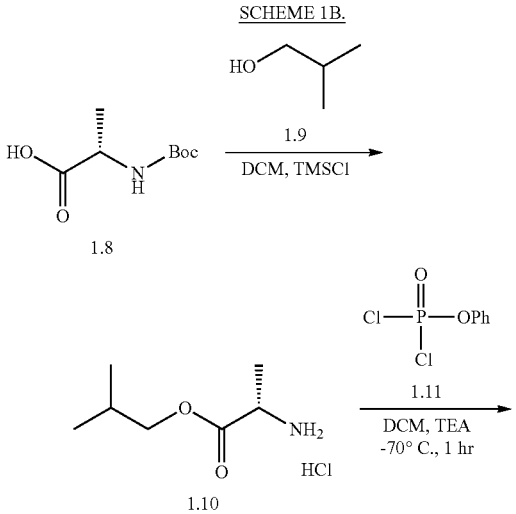
[0345] In one aspect, 4'-thio-nucleotide prodrug analogs can be prepared as shown below.

SCHEME 1A.



[0346] Compounds are represented in generic form, wherein LG is a leaving group and with other substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 1B.



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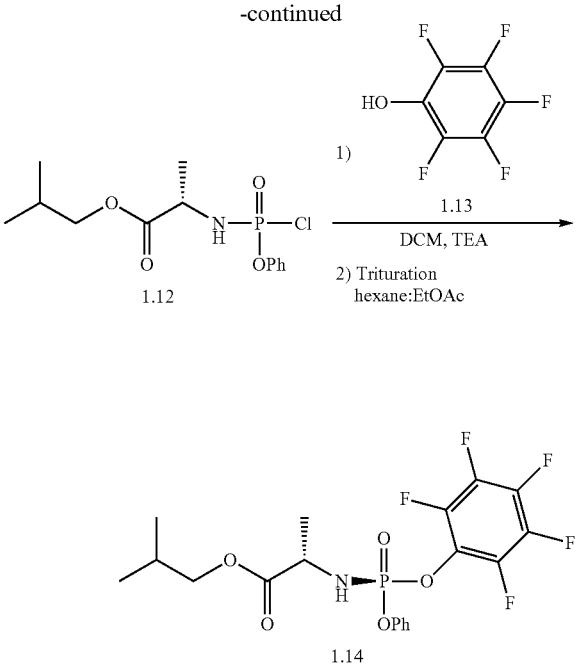
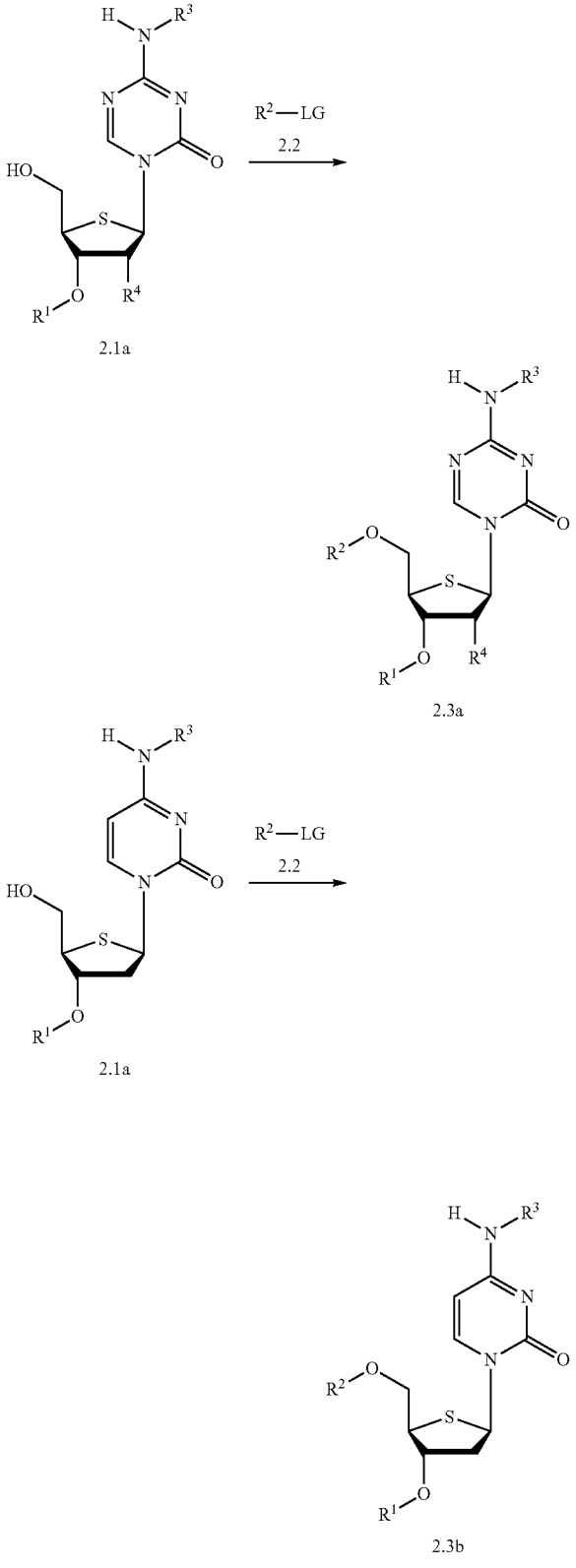


[0347] In one aspect, compounds of type 1.14, and similar compounds, can be prepared according to reaction Scheme 1B above. Thus, compounds of type 1.10 can be prepared by an alkylation reaction of an appropriate carboxylic acid, e.g., 1.8 as shown above. Appropriate carboxylic acids are commercially available or prepared by methods known to one skilled in the art. The alkylation reaction is carried out in the presence of an appropriate alcohol, e.g., 1.9 as shown above, and an appropriate activating agent, e.g., trimethylsilyl chloride as shown above, in an appropriate solvent, e.g., dichloromethane. Compounds of type 1.12 can be prepared by a phosphorylation between an appropriate amine, e.g., 1.10 as shown above, and an appropriate halophosphate, e.g., 1.11 as shown above. Appropriate halophosphates are commercially available or prepared by methods known to one skilled in the art. The phosphorylation is carried out in the presence of an appropriate base, e.g., triethylamine, in an appropriate solvent, e.g., dichloromethane, at an appropriate temperature, e.g., −70° C., for an appropriate period of time, e.g., 1 hour. Compounds of type 1.14 can be prepared by a substitution reaction of an appropriate electrophile, e.g., 1.12 as shown above. The substitution reaction is carried out in the presence of an appropriate nucleophile, e.g., 1.13 as shown above, and an appropriate base, e.g., triethylamine, in an appropriate solvent, e.g., dichloromethane, followed by trituration in an appropriate solvent system, e.g., hexanes: ethyl acetate. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type 1.1, 1.2, 1.3, 1.4, 1.5, and 1.6), can be substituted in the reaction to provide analogs similar to Formula 1.7.

[0348] 2. Route II

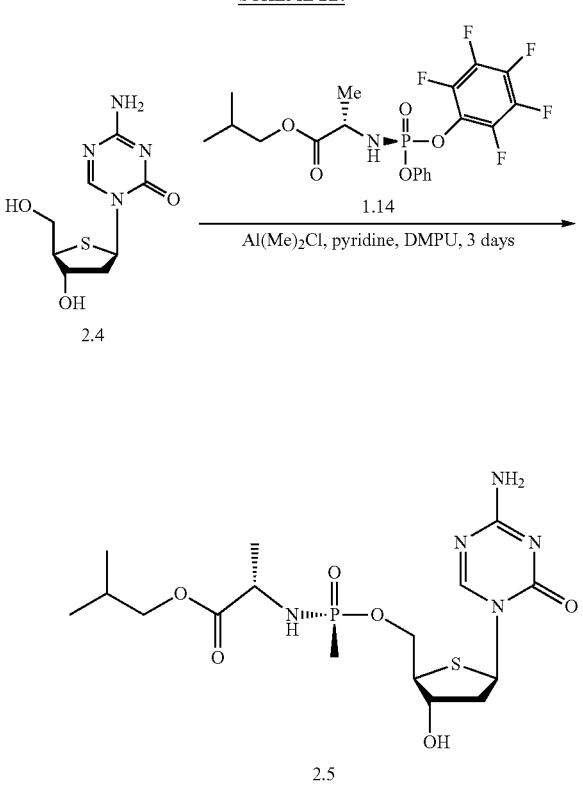
[0349] In one aspect, 4'-thio-nucleotide and nucleoside prodrug analogs can be prepared as shown below.

SCHEME 2A.



[0350] Compounds are represented in generic form, wherein LG is a leaving group and with other substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 2B.

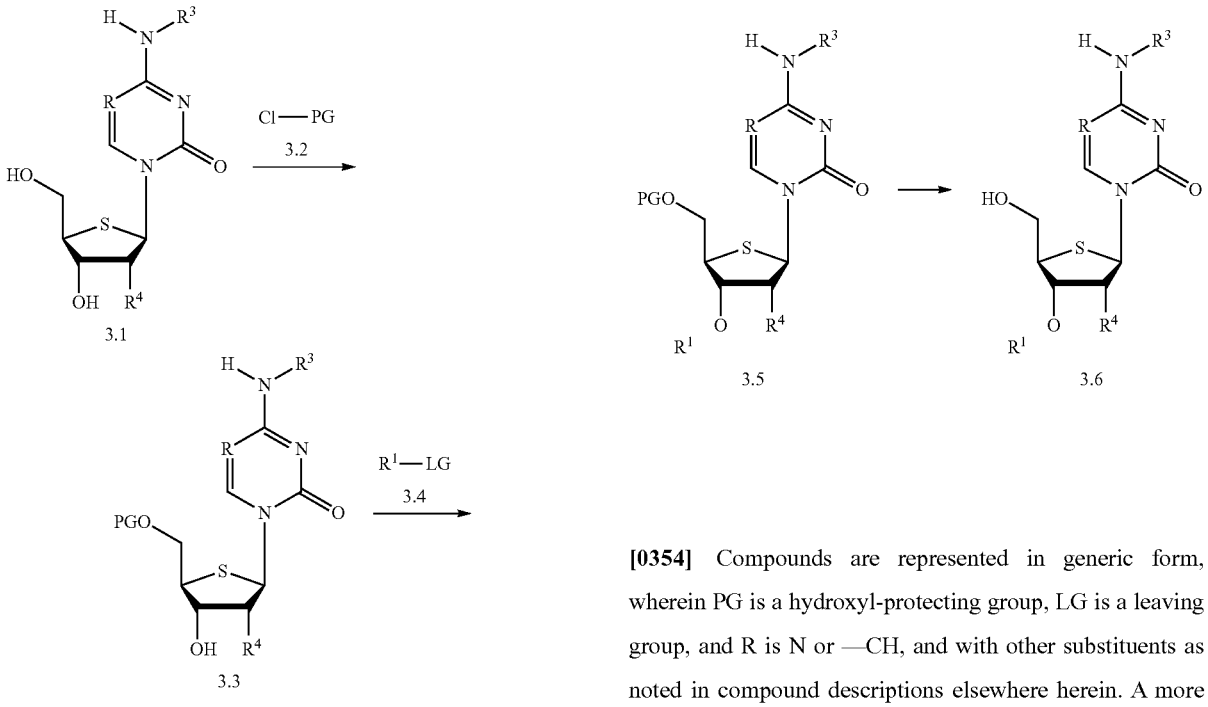


[0351] In one aspect, compounds of type 2.5, and similar compounds, can be prepared according to reaction Scheme 2B above. Thus, compounds of type 2.5 can be prepared by a substitution reaction of an appropriate nucleophile, e.g., 2.4 as shown above, and an appropriate electrophile, e.g., 1.14 as shown above. Appropriate nucleophiles are commercially available or prepared by methods known to one skilled in the art. The substitution reaction is carried out in the presence of an appropriate Lewis acid, e.g., $Al(Me)_2C1$, and an appropriate base, e.g., 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), in an appropriate solvent, e.g., pyridine, for an appropriate period of time, e.g., three days. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type 2.1a, 2.1b, and 2.2), can be substituted in the reaction to provide 4'-thio-nucleotide and nucleoside prodrug analogs similar to Formula 2.3a and 2.3b.

[0352] 3. Route III

[0353] In one aspect, 4'-thio-nucleotide and nucleoside prodrug analogs can be prepared as shown below.

SCHEME 3A.



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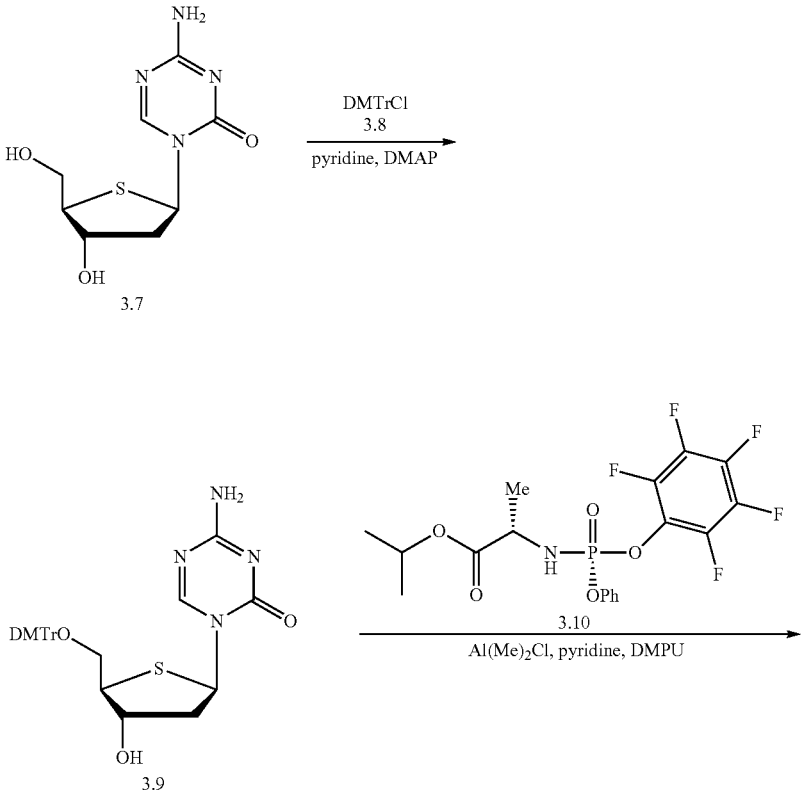
[0354] Compounds are represented in generic form, wherein PG is a hydroxyl-protecting group, LG is a leaving group, and R is N or —CH, and with other substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 3B.



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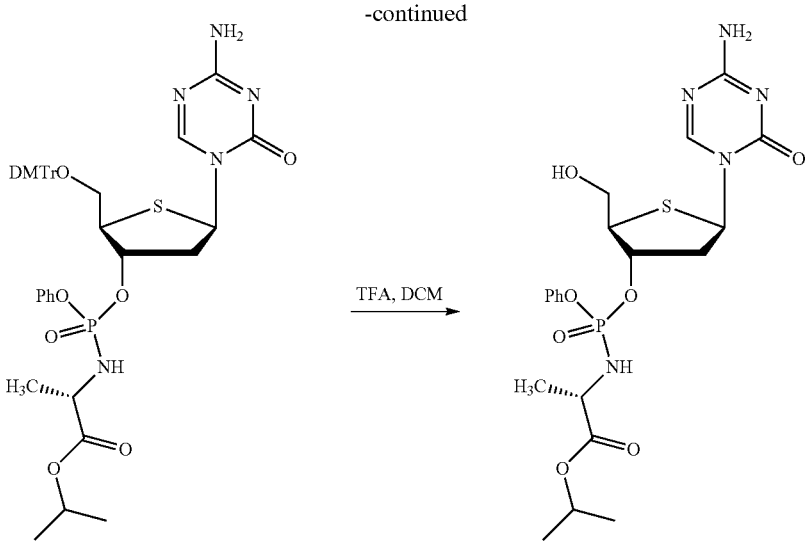


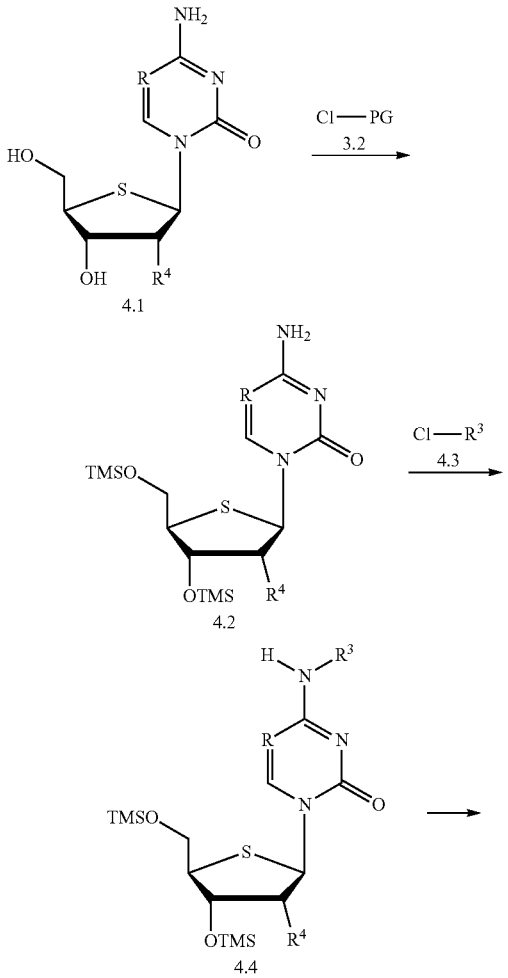
3.11 3.12

[0355] In one aspect, compounds of type 3.12, and similar compounds, can be prepared according to reaction Scheme 3B above. Thus, compounds of type 3.9 can be prepared by protection of an appropriate alcohol, e.g., 3.7 as shown above, with an appropriate hydroxyl protecting group agent, e.g., 3.8 as shown above. Appropriate hydroxyl protecting group agents are commercially available or prepared by methods known to one skilled in the art. The protection is carried out in the presence of an appropriate base, e.g., 4-dimethylaminopyridine, in an appropriate solvent, e.g., pyridine. Compounds of type 3.11 can be prepared by a substitution reaction of an appropriate nucleophile, e.g., 3.9 as shown above, and an appropriate electrophile, e.g., 3.10 as shown above. Appropriate nucleophiles are commercially available or prepared by methods known to one skilled in the art. The substitution reaction is carried out in the presence of an appropriate Lewis acid, e.g., $Al(Me)_2Cl$, and an appropriate base, e.g., 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), in an appropriate solvent, e.g., pyridine, for an appropriate period of time, e.g., three days. Compounds of type 3.12 can be prepared by deprotection of an appropriate protected alcohol, e.g., 3.11 as shown above. The deprotection is carried out in the presence of an appropriate deprotecting agent, e.g., trifluoroacetic acid as shown above, in an appropriate solvent, e.g., dichloromethane as shown above. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type 3.1, 3.2, 3.3, 3.4, and 3.5), can be substituted in the reaction to provide 4'-thio-nucleotide and -nucleoside prodrug analogs similar to Formula 3.6.

[0356] 4. Route IV

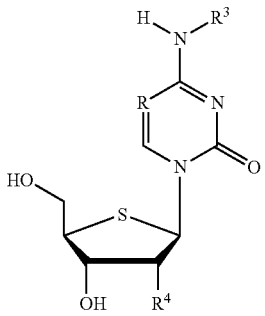
[0357] In one aspect, 4'-thio-nucleotide and nucleoside prodrug analogs can be prepared as shown below.

SCHEME 4A.



4.1 4.2 4.4

-continued



4.5

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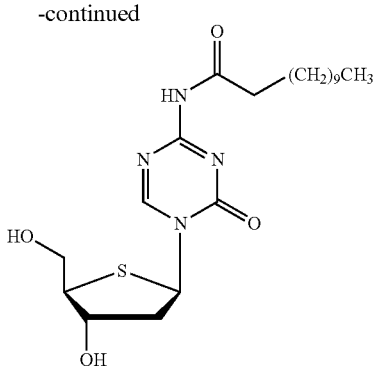
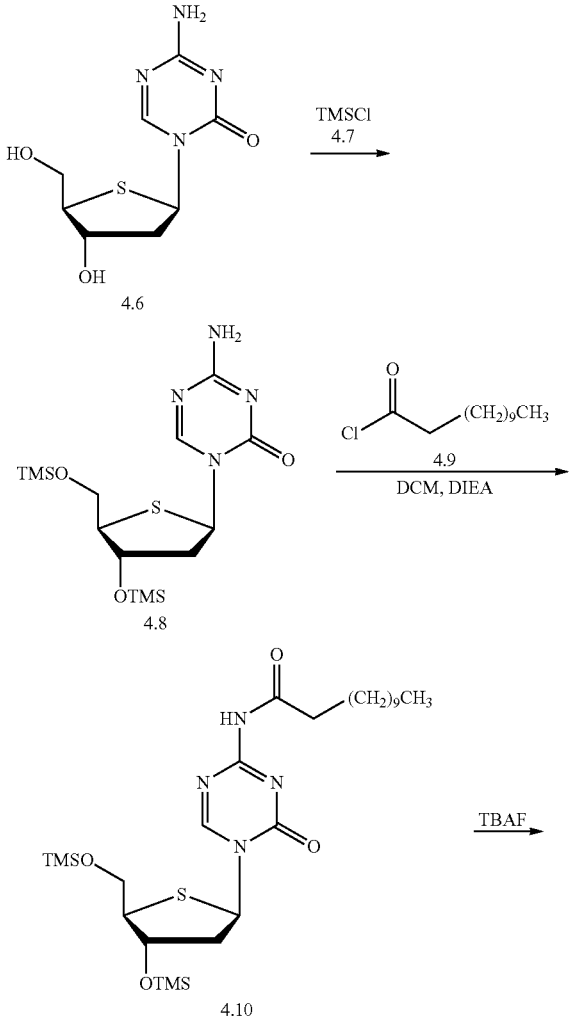


4.11

[0358] Compounds are represented in generic form, wherein PG is a hydroxyl-protecting group and R is N or —CH, and with other substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 4B.

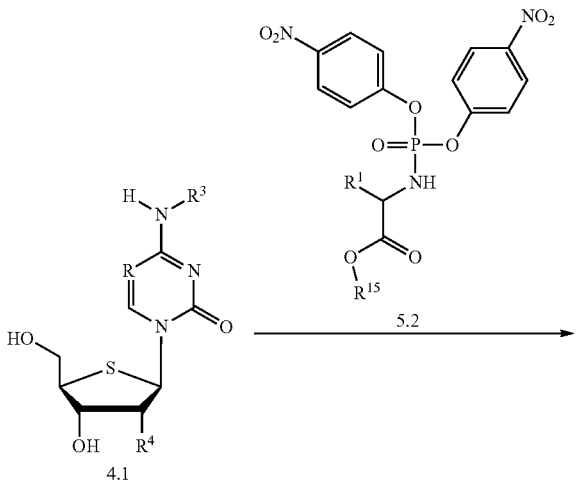


[0359] In one aspect, compounds of type 4.11, and similar compounds, can be prepared according to reaction Scheme 4B above. Thus, compounds of type 4.8 can be prepared by protection of an appropriate alcohol, e.g., 4.6 as shown above. Appropriate alcohols are commercially available or prepared by methods known to one skilled in the art. The protection is carried out in the presence of an appropriate alcohol protecting group agent, e.g., trimethylsilyl chloride. Compounds of type 4.10 can be prepared by an alkylation or acylation reaction of an appropriate amine, e.g., 4.8 as shown above. The alkylation or acylation is carried out in the presence of an appropriate alkylating agent or acylating agent, e.g., 4.9 as shown above, and an appropriate base, e.g., N,N-diisopropylethylamine as shown above, in an appropriate solvent, e.g., dichloromethane as shown above. Compounds of type 4.11 can be prepared by deprotection of an appropriate protected alcohol, e.g., 4.10 as shown above. The deprotection is carried out in the presence of an appropriate deprotecting agent, e.g., tetrabutylammonium fluoride as shown above. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type 3.2, 4.1, 4.2, 4.3, and 4.4), can be substituted in the reaction to provide 4'-thio-nucleotide and -nucleoside prodrug analogs similar to Formula 4.5.

[0360] 5. Route V

[0361] In one aspect, 4'-thio-nucleotide and nucleoside prodrug analogs can be prepared as shown below.

SCHEME 5A.



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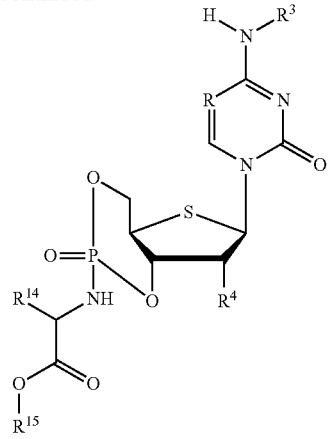
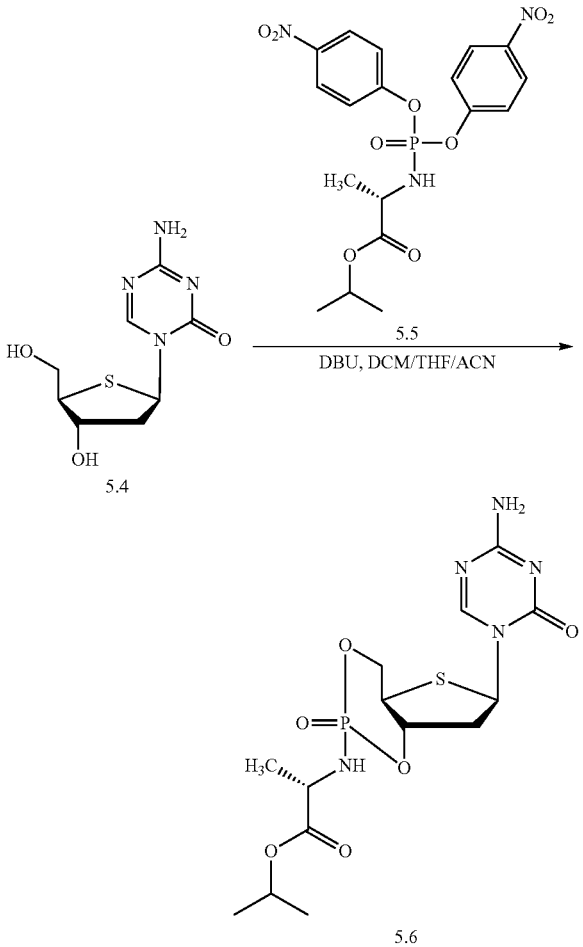


5.3

[0362] Compounds are represented in generic form, wherein R is N or CH and with other substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 5B.



5.4

5.5

DBU, DCM/THF/ACN

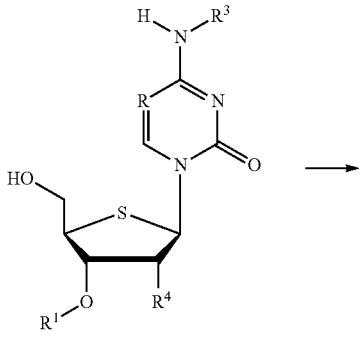
5.6

[0363] In one aspect, compounds of type 5.6, and similar compounds, can be prepared according to reaction Scheme 5B above. Thus, compounds of type 5.6 can be prepared by a substitution reaction of an appropriate dinucleophile, e.g., 5.4 as shown above, and an appropriate dielectrophile, e.g., 5.5 as shown above. Appropriate dinucleophiles and appropriate dielectrophiles are commercially available or prepared by methods known to one skilled in the art. The substitution reaction is carried out in the presence of an appropriate base, e.g., 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), in an appropriate solvent system, e.g., dichloromethane/tetrahydrofuran/acetonitrile. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type 5.1 and 5.2), can be substituted in the reaction to provide 4'-thio-nucleotide and -nucleoside prodrug analogs similar to Formula 3.1.

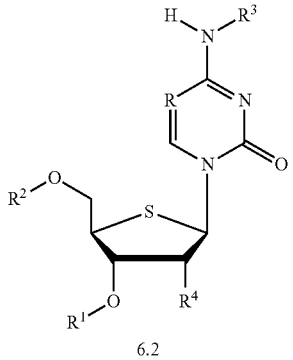
[0364] 6. Route VI

[0365] In one aspect, 4'-thio-nucleotide and nucleoside prodrug analogs can be prepared as shown below.

SCHEME 6A.



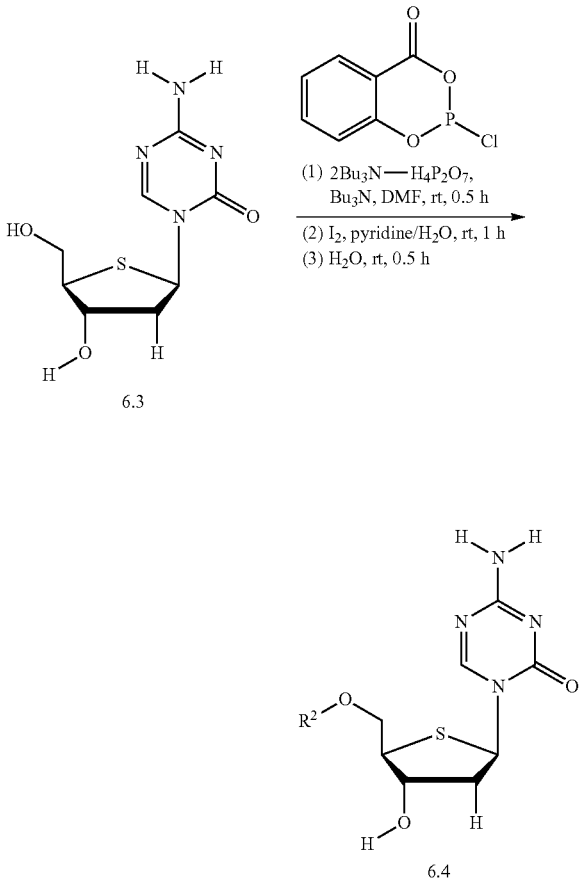
6.1



6.2

[0366] Compounds are represented in generic form, wherein R is C or N, R^2 is —P(O)(OH)OP(O)(OH)OP(O)$(OH)_2$, and with other substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

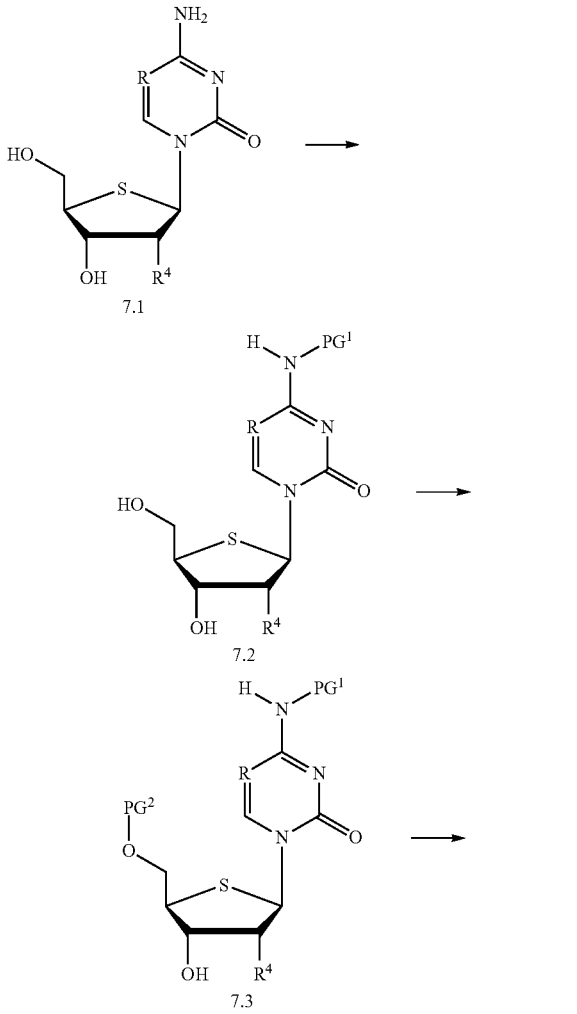
SCHEME 6B.



6.3

6.4

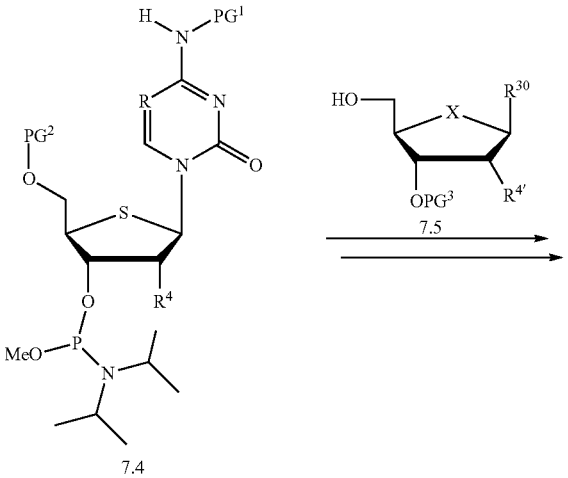
SCHEME 7A.



7.1

7.2

7.3



7.4

7.5

[0367] In one aspect, compounds of type 6.4, and similar compounds, can be prepared according to reaction Scheme 6B above. Thus, compounds of type 6.3 can be prepared by a substitution reaction with 2-chloro-4H-benzo[d][1,3,2]dioxaphosphinin-4-one as shown above. The substitution reaction is carried out in the presence of an appropriate oxidizing agent, e.g., pyrophosphoric acid, ammonium salt, in an appropriate solvent, e.g., dimethylformamide, for an appropriate period of time, e.g., 30 minutes. The substitution reaction is followed by hydrolysis using, for example, iodine in pyridine and water. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type 6.1a and 6.1b), can be substituted in the reaction to provide 4'-thio-nucleotide and -nucleoside prodrug analogs similar to Formula 6.2a and 6.2b.

[0368] 7. Route VII

[0369] In one aspect, 4'-thio-nucleotide and nucleoside prodrug analogs can be prepared as shown below.

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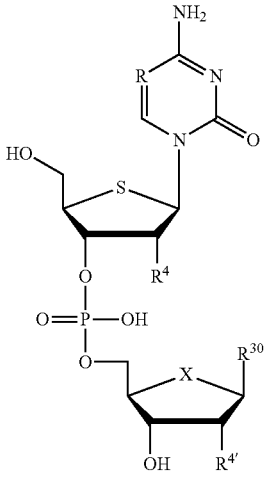

7.6

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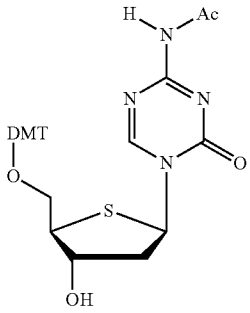
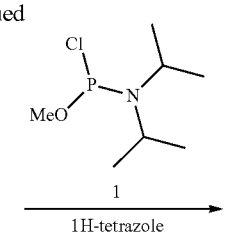
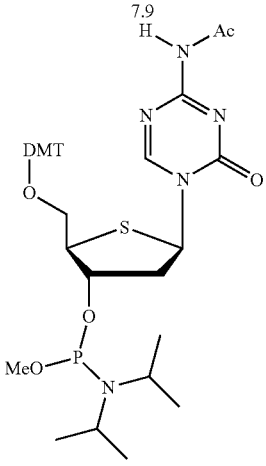


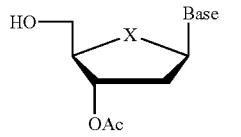


1

1H-tetrazole

7.9





7.11

1) I_2, 2,6-lutidine

2) Cl_3CO_2H, DCM

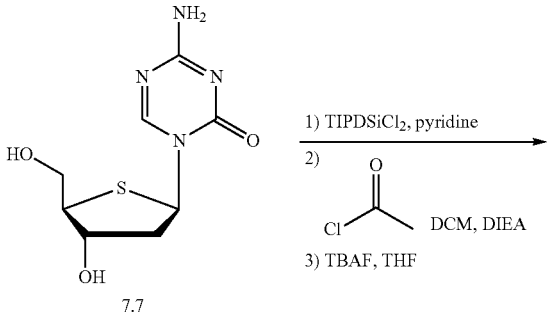
3) NH_4OH

Base = pyrimidine or purine base

7.10

[0370] Compounds are represented in generic form, wherein PG' is an amine protecting group, each of PG^2 and PG^3 are independently an alcohol protecting group, R is CH or N, and with other substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 7B.



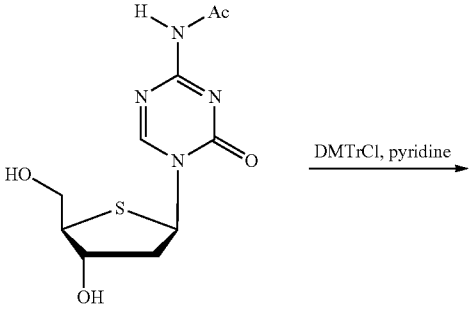
1) $TIPDSiCl_2$, pyridine

2)

DCM, DIEA

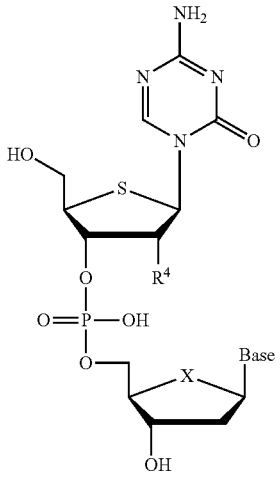
3) TBAF, THF

7.7



DMTrCl, pyridine

7.8



7.12

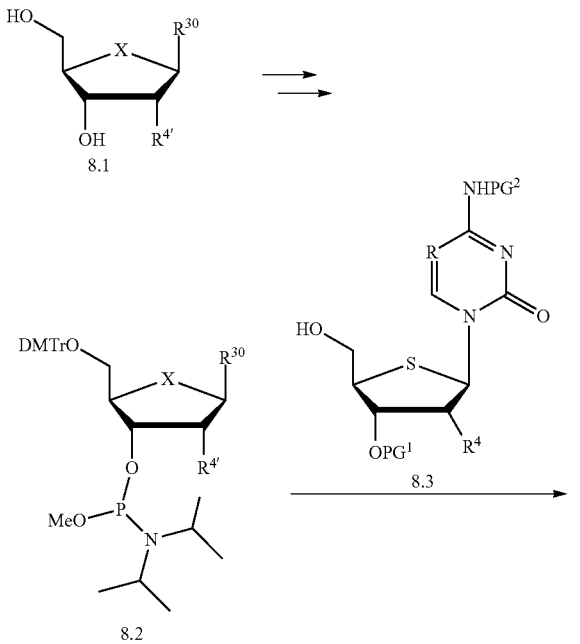
[0371] In one aspect, compounds of type 7.6, and similar compounds, can be prepared according to reaction Scheme 7B above. Thus, compounds of type 7.8 can be prepared by protection of an appropriate amine, e.g., 7.7 as shown above. The protection is carried out by first protecting the primary alcohol using an appropriate alcohol protecting agent, e.g., 1,3-chloro-1,1,3,3-tetraisopropyl-1,3-disiloxane, and an appropriate base, e.g., pyridine, followed by protection of the amine using an appropriate amine protecting agent, e.g., acetyl chloride, and an appropriate base, e.g., N,N-diisopropylethylamine, in an appropriate solvent, e.g., dichloromethane. The alcohol-protecting group is then removed using an

appropriate deprotecting agent, e.g., tetra-n-butylammonium fluoride (TBAF) in the presence of an appropriate solvent, e.g., tetrahydrofuran (THF). Compounds of type 7.9 can be prepared by protection of an appropriate alcohol, e.g., 7.8 as shown above. The protection is carried out in the presence of an appropriate protecting agent, e.g., 4,4'-dimethoxytrityl chloride, and an appropriate base, e.g., pyridine. Compounds of type 7.10 can be prepared by phosphorylation of an appropriate secondary alcohol, e.g., 7.9 as shown above. The reaction is carried out in the presence of an appropriate phosphorylating agent, e.g., 1-chloro-N,N-diisopropyl-1-methoxyphosphanamine, and an appropriate base, e.g., 1H-tetrazole. Compounds of type 7.12 can be prepared by oxidation of an appropriate phosphonite, e.g., 7.10 as shown above. The oxidation reaction is carried out in the presence of an appropriate nucleoside, e.g., 7.11 as shown above, an appropriate electrophile, e.g., iodine, and an appropriate base, e.g., 2,6-lutidine. The oxidation is followed by deprotection of the alcohol using an appropriate acid, e.g., trichloroacetic acid in dichloromethane, and deprotection of the amine using an appropriate base, e.g., ammonium hydroxide. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type 7.1, 7.2, 7.3, 7.4, 7.5, and 7.6), can be substituted in the reaction to provide 4'-thio-nucleotide and -nucleoside prodrug analogs similar to Formula 7.7.

[0372] 8. Route VIII

[0373] In one aspect, 4'-thio-nucleotide and nucleoside prodrug analogs can be prepared as shown below.

SCHEME 8A.



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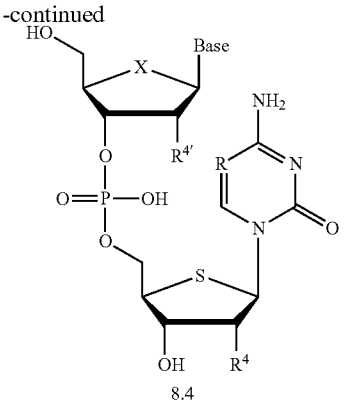
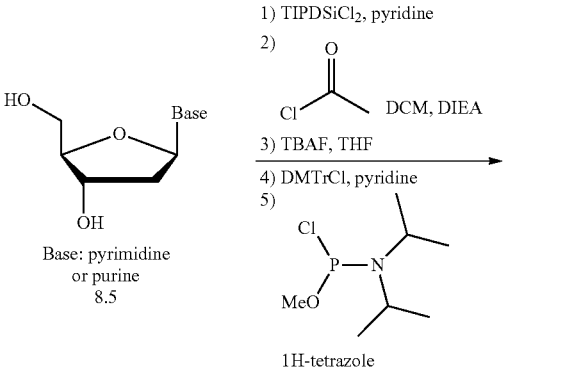
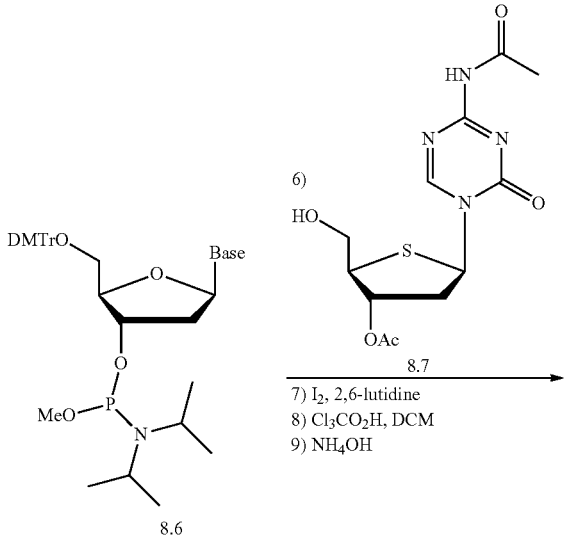


[0374] Compounds are represented in generic form, wherein R is N or CH, PG^1 is an alcohol protecting group, PG^2 is an amine protecting group, and with other substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 8B.





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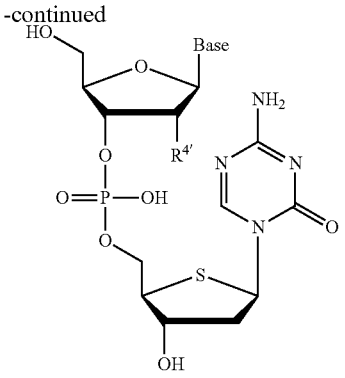


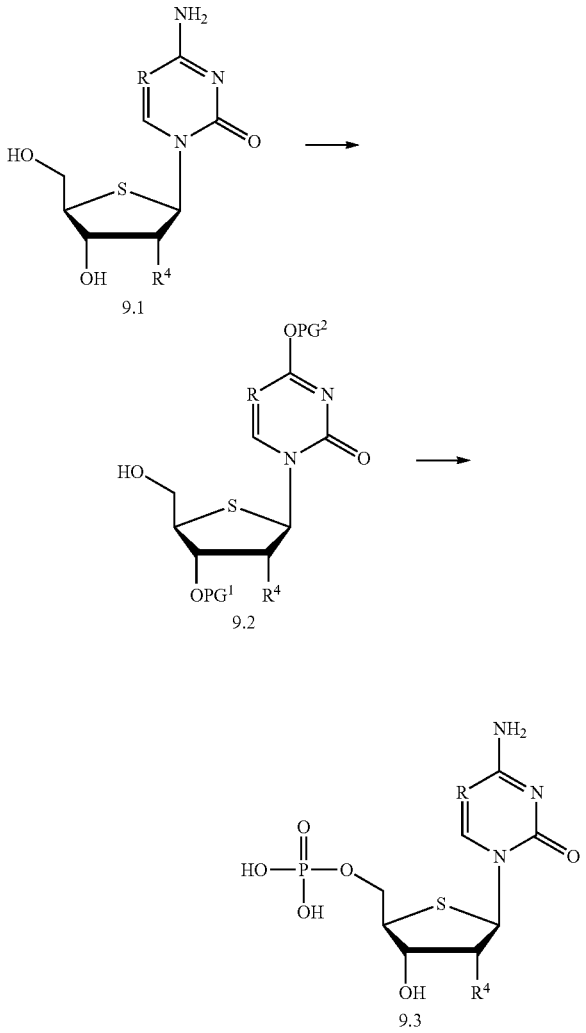
8.8

[0375] In one aspect, compounds of type 8.4, and similar compounds, can be prepared according to reaction Scheme 8B above. Thus, compounds of type 8.6 can be prepared by phosphorylation of an appropriate secondary alcohol, e.g., 8.5 as shown above. To carry out the phosphorylation, the primary alcohol can be first protected using an appropriate alcohol protecting agent, e.g., 1,3-chloro-1,1,3,3-tetraisopropyl-1,3-disiloxane, and an appropriate base, e.g., pyridine, followed by protection of the free amine on the base using an appropriate amine protecting agent, e.g., acetyl chloride, and an appropriate base, e.g., N,N-diisopropylethylamine, in an appropriate solvent, e.g., dichloromethane. The alcohol-protecting group is then removed using an appropriate deprotecting agent, e.g., tetra-n-butylammonium fluoride (TBAF) in the presence of an appropriate solvent, e.g., tetrahydrofuran (THF). Next, the primary alcohol is protected using an appropriate protecting agent, e.g., 4,4'-dimethoxytrityl chloride, and an appropriate base, e.g., pyridine. Finally, the phorphorylation reaction is carried out in the presence of an appropriate phosphorylating agent, e.g., 1-chloro-N,N-diisopropyl-1-methoxyphosphanamine, and an appropriate base, e.g., 1H-tetrazole. Compounds of type 8.8 can be prepared by oxidation of an appropriate phosphonite, e.g., 8.6 as shown above. The oxidation reaction is carried out in the presence of an appropriate nucleoside, e.g., 8.7 as shown above, an appropriate electrophile, e.g., iodine, and an appropriate base, e.g., 2,6-lutidine. The oxidation is followed by deprotection of the alcohol using an appropriate acid, e.g., trichloroacetic acid in dichloromethane, and deprotection of the amine using an appropriate base, e.g., ammonium hydroxide. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type 8.1, 8.2, and 8.3), can be substituted in the reaction to provide 4'-thio-nucleotide and -nucleoside prodrug analogs similar to Formula 8.4.

[0376] 9. Route IX

[0377] In one aspect, 4'-thio-nucleotide and nucleoside prodrug analogs can be prepared as shown below.

SCHEME 9A.



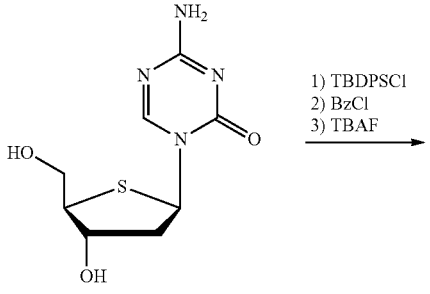
9.1

9.2

9.3

[0378] Compounds are represented in generic form, wherein PG' is an alcohol protecting group, PG^2 is an amine protecting group, R is N or CH, and with other substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

SCHEME 9B.



9.4

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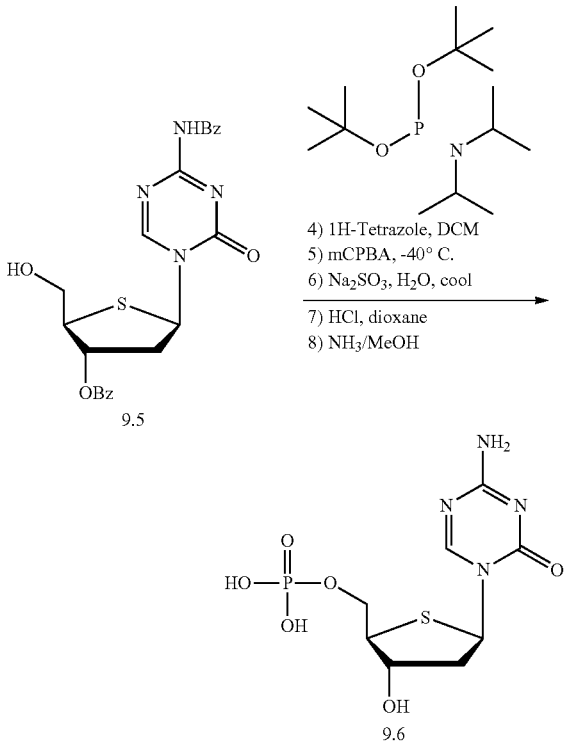


[0379] In one aspect, compounds of type 9.3, and similar compounds, can be prepared according to reaction Scheme 9B above. Thus, compounds of type 9.5 can be prepared by protection of an appropriate thionucleoside analog, e.g., 9.4 as shown above. The protection is carried out by first protecting the primary alcohol with an appropriate alcohol protecting group, e.g., tert-butyldiphenyl silyl chloride (TBDPSCl), followed by protection of the amine and the secondary alcohol with an appropriate protecting group, e.g., benzoyl chloride. Finally, the primary alcohol can be deprotected using an appropriate deprotecting agent, e.g., tetrabutyl ammonium fluoride. Compounds of type 9.6 can be prepared by phosphorylation of an appropriate nucleoside, e.g., 9.5 as shown above. The phosphorylation is carried out in the presence of an appropriate phosphorylating agent, e.g., di-tert-butyl diisopropylphosphoramidite, and an appropriate base, e.g., 1H-tetrazole. Next, the resultant phosphorylated compound is oxidized using an appropriate oxidizing agent, e.g., meta-chloroperoxybenzoic acid, at an appropriate temperature, e.g., −40° C. The reaction can then be quenched with an appropriate quenching agent, e.g., sodium sulphite, and the resultant compound protonated via addition of an appropriate acid, e.g., hydrochloric acid as shown above. Finally, the resultant nucleotide analog can be deprotected using an appropriate deprotecting agent, e.g., ammonia in methanol. As can be appreciated by one skilled in the art, the above reaction provides an example of a generalized approach wherein compounds similar in structure to the specific reactants above (compounds similar to compounds of type 9.1 and 9.2), can be substituted in the reaction to provide 4'-thio-nucleotide and -nucleoside prodrug analogs similar to Formula 9.3.

E. Methods of Using the Compounds

[0380] The compounds and pharmaceutical compositions of the invention are useful in treating or controlling disorders associated with uncontrolled cellular proliferation and in particular, cancer.

[0381] Examples of disorders of uncontrolled cellular proliferation for which the compounds and compositions can be useful in treating, include, but are not limited to, cancers such as, for example, sarcomas, carcinomas, hematological cancers, solid tumors, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanomas, gliomas, leukemias, lymphomas, chronic myeloproliferative disorders, myelodysplastic syndromes, myeloproliferative neoplasms, and plasma cell neoplasms (myelomas).

[0382] To treat or control the disorder, the compounds and pharmaceutical compositions comprising the compounds are administered to a subject in need thereof, such as a vertebrate, e.g., a mammal, a fish, a bird, a reptile, or an amphibian. The subject can be a human, non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig or rodent. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered. The subject is preferably a mammal, such as a human. Prior to administering the compounds or compositions, the subject can be diagnosed with a need for treatment of a disorder of uncontrolled cellular proliferation, such as cancer.

[0383] The compounds or compositions can be administered to the subject according to any method. Such methods are well known to those skilled in the art and include, but are not limited to, oral administration, transdermal administration, administration by inhalation, nasal administration, topical administration, intravaginal administration, ophthalmic administration, intraaural administration, intracerebral administration, rectal administration, sublingual administration, buccal administration and parenteral administration, including injectable such as intravenous administration, intra-arterial administration, intramuscular administration, and subcutaneous administration. Administration can be continuous or intermittent. A preparation can be administered therapeutically; that is, administered to treat an existing disease or condition. A preparation can also be administered prophylactically; that is, administered for prevention of a disorder of uncontrolled cellular proliferation, such as cancer.

[0384] The therapeutically effective amount or dosage of the compound can vary within wide limits. Such a dosage is adjusted to the individual requirements in each particular case including the specific compound(s) being administered, the route of administration, the condition being treated, as well as the patient being treated. In general, in the case of oral or parenteral administration to adult humans weighing approximately 70 Kg or more, a daily dosage of about 10 mg to about 10,000 mg, preferably from about 200 mg to about 1,000 mg, should be appropriate, although the upper limit may be exceeded. The daily dosage can be administered as a single dose or in divided doses, or for parenteral administration, as a continuous infusion. Single dose compositions can contain such amounts or submultiples thereof of the compound or composition to make up the daily dose. The dosage can be adjusted by the individual physician in the

event of any contraindications. Dosage can vary, and can be administered in one or more dose administrations daily, for one or several days.

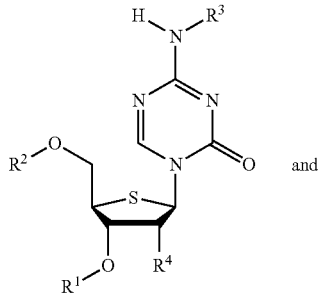
[0385] 1. Treatment Methods

[0386] The compounds disclosed herein are useful for treating or controlling disorders associated with uncontrolled cellular proliferation, in particular, cancer. Thus, provided is a method comprising administering a therapeutically effective amount of a composition comprising a disclosed compound to a subject. In a further aspect, the method can be a method for treating a disorder of uncontrolled cellular proliferation.

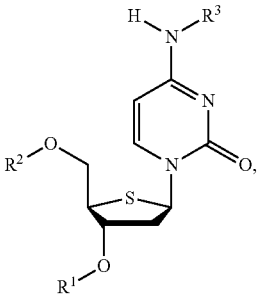
[0387] a. Treating a Disorder of Uncontrolled Cellular Proliferation

[0388] In one aspect, disclosed are methods of treating a disorder of uncontrolled cellular proliferation in a subject having the disorder, the method comprising the step of administering to the subject a therapeutically effective amount of at least one disclosed compound, or a pharmaceutically acceptable salt thereof.

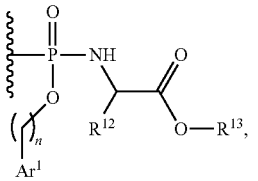
[0389] In one aspect, disclosed are methods for treating a disorder of uncontrolled cellular proliferation in a subject, the method comprising the step of administering to the subject an effective amount of a compound having a structure represented by a formula selected from:



and



wherein each of R^1 and R^2 is independently selected from hydrogen, —$C(O)R^{10}$, —$P(O)(OR^{11})_2$, —$P(O)(OH)OP(O)(OH)OP(O)(OH)_2$, and a structure represented by a formula selected from:



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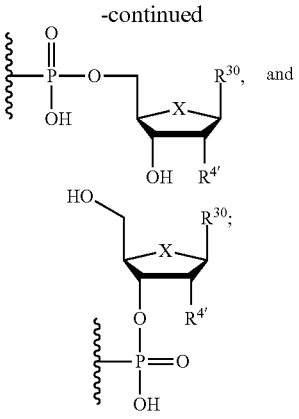
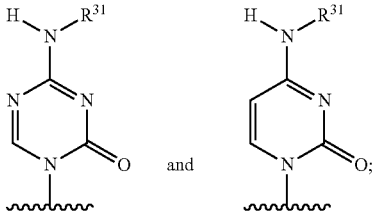
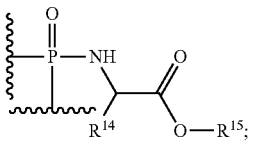


and

provided that one of R^1 and R^2 is hydrogen; wherein n is selected from 0, 1, and 2; wherein X, when present, is selected from O and S; wherein R^{10}, when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and —$CH(NH_2)R^{20}$; wherein R^{20}, when present, is selected from hydrogen, methyl, isopropyl, isobutyl, sec-butyl, —$(CH_2)_3NHC(NH)NH_2$, —$(CH_2)_4NH_2$, —CH_2CO_2H, —$(CH_2)_2CO_2H$, —CH_2OH, —$CH(OH)CH_3$, —$CH_2C(O)NH_2$, —$(CH_2)_2C(O)NH_2$, —CH_2SH, —$(CH_2)_2SCH_3$, —CH_2SeH, —$CH_2C_6H_5$, and —CH_2Cy^1; wherein Cy^1, when present, is selected from monocylic aryl, para-hydroxy monocyclic aryl, 4-imidazolyl, and 3-indolyl; wherein each occurrence of R^{11}, when present, is independently selected from hydrogen, -(C1-C10 alkyl)CO_2(C1-C10 alkyl), —(C1-C10 alkoxy)CO_2(C1-C10 alkyl), —(C1-C10 alkyl)CO_2(C1-C10 alkylthio), —(C1-C10 alkyl)-S—S—(C1-C10 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH; wherein Ar^2, when present, is selected from aryl and heteroaryl substituted with 1 or 2 groups independently selected from C1-C10 alkyl and nitro; wherein R^{12}, when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylamino, —(C1-C8)C(O)NH_2, aryl, and —(CH_2)aryl; wherein R^{13}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar^3; wherein Ar^3, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino; wherein Ar^1, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino; wherein R^{30}, when present, is a structure selected from:



wherein R^{31}, when present, is selected from hydrogen, —C(O)(C1-C30 alkyl), and —C(O)(C2-C30 alkenyl); or wherein each of R^1 and R^2 together comprise a structure represented by a formula:



wherein R^{14}, when present, is C1-C8 alkyl; wherein R^{15}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and aryl substituted with 0 or 1 C1-C10 alkyl groups; wherein R^3 is selected from hydrogen, —C(O)(C1-C30 alkyl), and —C(O)(C2-C30 alkenyl); wherein each of R^4 and $R^{4'}$, when present, is independently selected from hydrogen, fluoro, —CN, C2-C4 alkenyl, C2-C4 alkynyl, C1-C4 haloalkyl, and —OR^{16}; and wherein R^{16}, when present, is selected from hydrogen, methyl, and —$C(O)R^{10}$, provided that R^1, R^2, and R^3 are not simultaneously hydrogen, or a pharmaceutically acceptable salt thereof.

[0390] Examples of disorders of uncontrolled cellular proliferation include, but are not limited to, cancers such as, for example, sarcomas, carcinomas, hematological cancers, solid tumors, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanomas, gliomas, leukemias, lymphomas, chronic myeloproliferative disorders, myelodysplastic syndromes, myeloproliferative neoplasms, and plasma cell neoplasms (myelomas).

[0391] In a further aspect, the subject has been diagnosed with a need for treatment of the disorder prior to the administering step.

[0392] In a further aspect, the subject is a mammal. In a still further aspect, the mammal is a human.

[0393] In a further aspect, the method further comprises the step of identifying a subject in need of treatment of the disorder of uncontrolled cellular proliferation.

[0394] In a further aspect, the disorder of uncontrolled cellular proliferation is the disorder is a cancer. In a still further aspect, the cancer is selected from a sarcoma, a carcinoma, a hematological cancer, a solid tumor, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanoma, glioma, leukemia, lymphoma, chronic myeloproliferative disorder, myelodysplastic syndrome, myeloproliferative neoplasm, and plasma cell neoplasm (myeloma). In yet a further aspect, the cancer is selected from a leukemia, colorectal cancer, pancreatic cancer, ovarian cancer, non-small cell lung carcinoma, and breast cancer. In an even further aspect, the cancer is a liver cancer. In a still further aspect, the liver cancer is selected from hepatocellular carcinoma, cholangiocarcinoma, and biliary tract cancer. In yet a further aspect, the liver cancer is a metastasis originated from another cancer.

[0395] In a further aspect, the effective amount is a therapeutically effective amount. In a still further aspect, the effective amount is a prophylactically effective amount.

[0396] In a further aspect, the method further comprises the step of administering a therapeutically effective amount of at least one agent associated with the treatment of a disorder of uncontrolled cellular proliferation. In a still further aspect, the at least one agent is a chemotherapeutic agent. In yet a further aspect, the chemotherapeutic agent is selected from an alkylating agent, an antimetabolite agent, an antineoplastic antibiotic agent, a mitotic inhibitor agent, and a mTor inhibitor agent. In an even further aspect, the at least one agent is a chemotherapeutic agent or an anti-neoplastic agent. In a still further aspect, the chemotherapeutic agent or anti-neoplastic agent is selected from kinase inhibitors, poly ADP ribose polymerase (PARP) inhibitors and other DNA damage response modifiers, epigenetic agents such as bromodomain and extra-terminal (BET) inhibitors, histone deacetylase (HDAc) inhibitors, iron chelotors and other ribonucleotides reductase inhibitors, proteasome inhibitors and Nedd8-activating enzyme (NAE) inhibitors, mammalian target of rapamycin (mTOR) inhibitors, traditional cytotoxic agents such as paclitaxel, dox, irinotecan, and platinum compounds, immune checkpoint blockade agents such as cytotoxic T lymphocyte antigen-4 (CTLA-4) monoclonal antibody (mAB), programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) mAB, cluster of differentiation 47 (CD47) mAB, toll-like receptor (TLR) agonists and other immune modifiers, cell therapeutics such as chimeric antigen receptor T-cell (CAR-T)/chimeric antigen receptor natural killer (CAR-NK) cells, and proteins such as interferons (IFNs), interleukins (ILs), and mAbs.

[0397] In a further aspect, the antineoplastic antibiotic agent is selected from doxorubicin, mitoxantrone, bleomycin, daunorubicin, dactinomycin, epirubicin, idarubicin, plicamycin, mitomycin, pentostatin, and valrubicin, or a pharmaceutically acceptable salt thereof.

[0398] In a further aspect, the antimetabolite agent is selected from gemcitabine, 5-fluorouracil, capecitabine, hydroxyurea, mercaptopurine, pemetrexed, fludarabine, nelarabine, cladribine, clofarabine, cytarabine, decitabine, pralatrexate, floxuridine, methotrexate, and thioguanine, or a pharmaceutically acceptable salt thereof.

[0399] In a further aspect, the alkylating agent is selected from carboplatin, cisplatin, cyclophosphamide, chlorambucil, melphalan, carmustine, busulfan, lomustine, dacarbazine, oxaliplatin, ifosfamide, mechlorethamine, temozolomide, thiotepa, bendamustine, and streptozocin, or a pharmaceutically acceptable salt thereof.

[0400] In a further aspect, the mitotic inhibitor agent is selected from irinotecan, topotecan, rubitecan, cabazitaxel, docetaxel, paclitaxel, etopside, vincristine, ixabepilone, vinorelbine, vinblastine, and teniposide, or a pharmaceutically acceptable salt thereof

[0401] In a further aspect, the mTor inhibitor agent is selected from everolimus, siroliumus, and temsirolimus, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[0402] In a further aspect, the kinase inhibitor is selected from p38 inhibitors, CDK inhibitors, TNF inhibitors, matrixmetallo proteinase (MMP) inhibitors, COX-2 inhibitors, including celecoxib, rofecoxib, parecoxib, valdecoxib, and etoricoxib, SOD mimics, and $\alpha_v\beta 3$-inhibitors.

[0403] In a further aspect, the PARP inhibitor is selected from iniparib, talazoparib, olaparib, rucapariv, veliparib, CEP 9722, AK 4827, BGB-290 and 3-aminobenzamide.

[0404] In a further aspect, the epigenetic agent is selected from a histone deacetylase inhibitor and a DNA methylation inhibitor. In a still further aspect, the epigenetic agent is a BET inhibitor. In yet a further aspect, the BET inhibitor is selected from JQ1, 1-BET 151 (GSK1210151A), I-BET 762 (GSK525762), OTX-015, TEN-010 (Tensha therapeutics), CPI-203, RVX-208 (Resverlogix Corp), LY294002, MK-8628 (Merck/Mitsubishi Tanabe), BMS-986158 (Bristol-Myers Squibb), INCB54329 (Incyte Pharmaceuticals), ABBV-075 (Abb Vie, also called ABV-075), CPI-0610 (Constellation Pharmaceuticals/Roche), FT-1101 (Forma Therapeutics/Celgene), GS-5829 (Gilead Sciences), and PLX51107 (Daiichi Sankyo).

[0405] In a further aspect, the HDAc inhibitor is selected from pracinostat and panobinostat.

[0406] In a further aspect, the ribonuclotide reductase inhibitor is selected from fludarabine, cladribine, gemcitabine, tezacitabine, triapine, motexafm gadolinium, hydroxyurea, gallium maltolate, and gallium nitrate. In a still further aspect, the ribonucleotide reductase inhibitor is an iron chelator.

[0407] In a further aspect, the proteasome inhibitor is selected from lactacystin and bortezomib.

[0408] In a further aspect, the NAE inhibitor is a 1-substituted methyl sulfamate. In a still further aspect, the NAE inhibitor is MLN4924.

[0409] In a further aspect, the immune checkpoint blockade agent is selected from anti-PD-L1 antibodies, anti-CTLA-4 antibodies, anti-PD-1 antibodies, anti-LAG3 antibodies, anti-B7-H3 antibodies, anti-TEVI3 antibodies, antibodies to PD-1, CTLA-4, BTLA, TIM-3, LAG-3, CD160, TIGIT, LAIR1, and 2B4, antibodies to the corresponding ligands for these receptors including, but not limited to, PD-L1 (for PD-1), PD-L2 (for PD-1), CD80 and CD86 (for CTLA-4), HVEM (for BTLA), Galectin-9 and HMGB1 (for TIM-3), MHC II (for LAG-3), HVEM (for CD160), CD155, CD112, and CD113 (for TIGIT), C1q and collagen (for LAIR1), and CD48 (for 2B4). In a still further aspect, the immune checkpoint blockade agent is selected from CTL-4 mAb, PD-1/PD-L1 mAB, and CD47 mAB.

[0410] In a further aspect, the TLR agonist is selected from CRX-527 and OM-174.

[0411] In a further aspect the cell therapeutic is selected from CAR-T cell therapy and CAR-NK cell therapy.

[0412] In a further aspect, the at least one compound and the at least one agent are administered sequentially. In a still further aspect, the at least one compound and the at least one agent are administered simultaneously.

[0413] In a further aspect, the at least one compound and the at least one agent are co-formulated. In a still further aspect, the at least one compound and the at least one agent are co-packaged.

[0414] 2. Use of Compounds

[0415] In one aspect, the invention relates to the use of a disclosed compound or a product of a disclosed method. In a further aspect, a use relates to the manufacture of a medicament for the treatment of a disorder of uncontrolled cellular proliferation in a subject.

[0416] Also provided are the uses of the disclosed compounds and products. In one aspect, the invention relates to use of at least one disclosed compound; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof. In a further aspect, the compound used is a product of a disclosed method of making.

[0417] In a further aspect, the use relates to a process for preparing a pharmaceutical composition comprising a therapeutically effective amount of a disclosed compound or a product of a disclosed method of making, or a pharmaceutically acceptable salt, solvate, or polymorph thereof, for use as a medicament.

[0418] In a further aspect, the use relates to a process for preparing a pharmaceutical composition comprising a therapeutically effective amount of a disclosed compound or a product of a disclosed method of making, or a pharmaceutically acceptable salt, solvate, or polymorph thereof, wherein a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of the compound or the product of a disclosed method of making.

[0419] In various aspects, the use relates to a treatment of a disorder of uncontrolled cellular proliferation in a subject. In one aspect, the use is characterized in that the subject is a human. In one aspect, the use is characterized in that the disorder is a disorder of uncontrolled cellular proliferation.

[0420] In a further aspect, the use relates to the manufacture of a medicament for the treatment of a disorder of uncontrolled cellular proliferation in a subject.

[0421] In a further aspect, the use relates to modulating viral activity in a subject. In a still further aspect, the use relates to modulating viral activity in a cell. In yet a further aspect, the subject is a human.

[0422] It is understood that the disclosed uses can be employed in connection with the disclosed compounds, products of disclosed methods of making, methods, compositions, and kits. In a further aspect, the invention relates to the use of a disclosed compound or a disclosed product in the manufacture of a medicament for the treatment of a disorder of uncontrolled cellular proliferation in a mammal. In a further aspect, the disorder of uncontrolled cellular proliferation is a cancer.

[0423] 3. Manufacture of a Medicament

[0424] In one aspect, the invention relates to a method for the manufacture of a medicament for treating a disorder of uncontrolled cellular proliferation in a subject having the disorder, the method comprising combining a therapeutically effective amount of a disclosed compound or product of a disclosed method with a pharmaceutically acceptable carrier or diluent.

[0425] As regards these applications, the present method includes the administration to an animal, particularly a mammal, and more particularly a human, of a therapeutically effective amount of the compound effective in the treatment of a disorder of uncontrolled cellular proliferation. The dose administered to an animal, particularly a human, in the context of the present invention should be sufficient to affect a therapeutic response in the animal over a reasonable time frame. One skilled in the art will recognize that dosage will depend upon a variety of factors including the condition of the animal and the body weight of the animal.

[0426] The total amount of the compound of the present disclosure administered in a typical treatment is preferably between about 0.05 mg/kg and about 100 mg/kg of body weight for mice, and more preferably between 0.05 mg/kg and about 50 mg/kg of body weight for mice, and between about 100 mg/kg and about 500 mg/kg of body weight, and more preferably between 200 mg/kg and about 400 mg/kg of body weight for humans per daily dose. This total amount is typically, but not necessarily, administered as a series of smaller doses over a period of about one time per day to

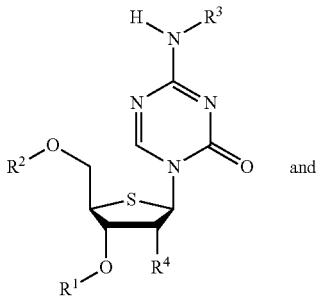
about three times per day for about 24 months, and preferably over a period of twice per day for about 12 months.

[0427] The size of the dose also will be determined by the route, timing, and frequency of administration as well as the existence, nature, and extent of any adverse side effects that might accompany the administration of the compound and the desired physiological effect. It will be appreciated by one of skill in the art that various conditions or disease states, in particular chronic conditions or disease states, may require prolonged treatment involving multiple administrations.

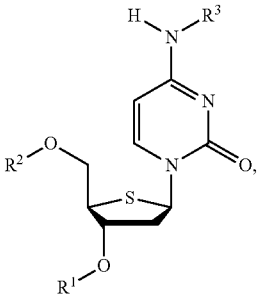
[0428] Thus, in one aspect, the invention relates to the manufacture of a medicament comprising combining a disclosed compound or a product of a disclosed method of making, or a pharmaceutically acceptable salt, solvate, or polymorph thereof, with a pharmaceutically acceptable carrier or diluent.

[0429] 4. Kits

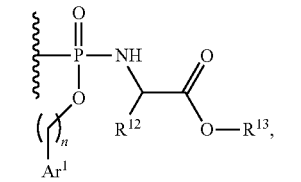
[0430] In one aspect, the invention relates to a kit comprising at least one compound having a structure represented by a formula selected from:



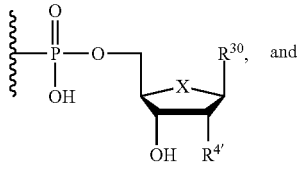
and



wherein each of R^1 and R^2 is independently selected from hydrogen, —C(O)R^{10}, —P(O)(OR^{11})$_2$, —P(O)(OH)OP(O)(OH)OP(O)(OH)$_2$, and a structure represented by a formula selected from:



and



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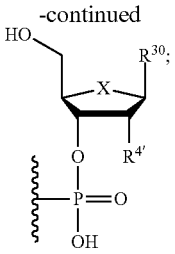
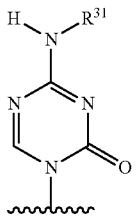
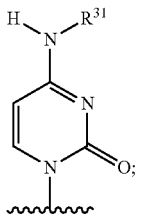


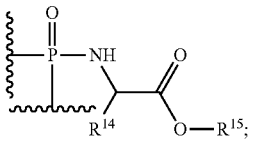
provided that one of R^1 and R^2 is hydrogen; wherein n is selected from 0, 1, and 2; wherein X, when present, is selected from O and S; wherein R^{10}, when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and —CH(NH_2)R^{20}; wherein R^{20}, when present, is selected from hydrogen, methyl, isopropyl, isobutyl, sec-butyl, —(CH_2)$_3$NHC(NH)NH_2, —(CH_2)$_4NH_2$, —CH_2CO_2H, —(CH_2)$_2CO_2H$, —CH_2OH, —CH(OH)CH_3, —$CH_2C(O)NH_2$, —(CH_2)$_2C(O)NH_2$, —CH_2SH, —(CH_2)$_2SCH_3$, —CH_2SeH, —$CH_2C_6H_5$, and —CH_2Cy^1; wherein Cy^1, when present, is selected from monocylic aryl, para-hydroxy monocyclic aryl, 4-imidazolyl, and 3-indolyl; wherein each occurrence of R^{11}, when present, is independently selected from hydrogen, —(C1-C10 alkyl)CO_2(C1-C10 alkyl), —(C1-C10 alkoxy)CO_2(C1-C10 alkyl), —(C1-C10 alkyl)CO_2(C1-C10 alkylthio), —(C1-C10 alkyl)-S—S—(C1-C10 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH; wherein Ar^2, when present, is selected from aryl and heteroaryl substituted with 1 or 2 groups independently selected from C1-C10 alkyl and nitro; wherein R^{12}, when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylamino, —(C1-C8)C(O)NH_2, aryl, and —(CH_2)aryl; wherein R^{13}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar^3; wherein Ar^3, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino; wherein Ar^1, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino; wherein R^{30}, when present, is a structure selected from:



and



wherein R^{31}, when present, is selected from hydrogen, —C(O)(C1-C30 alkyl), and —C(O)(C2-C30 alkenyl); or wherein each of R^1 and R^2 together comprise a structure represented by a formula:



wherein R^{14}, when present, is C1-C8 alkyl; wherein R^{15}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and aryl substituted with 0 or 1 C1-C10 alkyl groups; wherein R^3 is selected from hydrogen, —C(O)(C1-C30 alkyl), and —C(O)(C2-C30 alkenyl); wherein each of R^4 and $R^{4'}$, when present, is independently selected from hydrogen, fluoro, —CN, C2-C4 alkenyl, C2-C4 alkynyl, C1-C4 haloalkyl, and —OR^{16}; and wherein R^{16}, when present, is selected from hydrogen, methyl, and —$C(O)R^{10}$, provided that R^1, R^2, and R^3 are not simultaneously hydrogen, or a pharmaceutically acceptable salt thereof, and one or more of: (a) at least one agent associated with the treatment of a disorder of uncontrolled cellular proliferation; (b) instructions for administering the compound in connection with treating a disorder of uncontrolled cellular proliferation; and (c) instructions for treating a disorder of uncontrolled cellular proliferation.

[0431] In a further aspect, the disorder of uncontrolled cellular proliferation is a cancer. In a still further aspect, the cancer is selected from a sarcoma, a carcinoma, a hematological cancer, a solid tumor, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanoma, glioma, leukemia, lymphoma, chronic myeloproliferative disorder, myelodysplastic syndrome, myeloproliferative neoplasm, and plasma cell neoplasm (myeloma). In yet a further aspect, the cancer is selected from a leukemia, colorectal cancer, pancreatic cancer, ovarian cancer, non-small cell lung carcinoma, and breast cancer. In an even further aspect, the cancer is a liver cancer. In a still further aspect, the liver cancer is selected from hepatocellular carcinoma, cholangiocarcinoma, and biliary tract cancer. In yet a further aspect, the liver cancer is a metastasis originated from another cancer.

[0432] In a further aspect, the at least one agent is a chemotherapeutic agent. In yet a further aspect, the chemotherapeutic agent is selected from an alkylating agent, an antimetabolite agent, an antineoplastic antibiotic agent, a mitotic inhibitor agent, and a mTor inhibitor agent.

[0433] In a further aspect, the antineoplastic antibiotic agent is selected from doxorubicin, mitoxantrone, bleomycin, daunorubicin, dactinomycin, epirubicin, idarubicin, plicamycin, mitomycin, pentostatin, and valrubicin, or a pharmaceutically acceptable salt thereof.

[0434] In a further aspect, the antimetabolite agent is selected from gemcitabine, 5-fluorouracil, capecitabine, hydroxyurea, mercaptopurine, pemetrexed, fludarabine, nelarabine, cladribine, clofarabine, cytarabine, decitabine, pralatrexate, floxuridine, methotrexate, and thioguanine, or a pharmaceutically acceptable salt thereof.

[0435] In a further aspect, the alkylating agent is selected from carboplatin, cisplatin, cyclophosphamide, chlorambucil, melphalan, carmustine, busulfan, lomustine, dacarbazine, oxaliplatin, ifosfamide, mechlorethamine, temozolomide, thiotepa, bendamustine, and streptozocin, or a pharmaceutically acceptable salt thereof.

[0436] In a further aspect, the mitotic inhibitor agent is selected from irinotecan, topotecan, rubitecan, cabazitaxel, docetaxel, paclitaxel, etopside, vincristine, ixabepilone, vinorelbine, vinblastine, and teniposide, or a pharmaceutically acceptable salt thereof.

[0437] In a further aspect, the mTor inhibitor agent is selected from everolimus, siroliumus, and temsirolimus, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[0438] In a further aspect, the at least one compound and the at least one agent associated with the treatment of a disorder of uncontrolled cellular proliferation are co-formulated. In a further aspect, the at least one compound and the at least one agent associated with the treatment of a disorder of uncontrolled cellular proliferation are co-packaged.

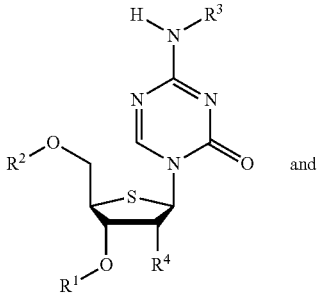
[0439] In a further aspect, the compound and the agent associated with the treatment of a disorder of uncontrolled cellular proliferation are administered sequentially. In a still further aspect, the compound and the agent associated with the treatment of a disorder of uncontrolled cellular proliferation are administered simultaneously.

[0440] The kits can also comprise compounds and/or products co-packaged, co-formulated, and/or co-delivered with other components. For example, a drug manufacturer, a drug reseller, a physician, a compounding shop, or a pharmacist can provide a kit comprising a disclosed compound and/or product and another component for delivery to a patient.

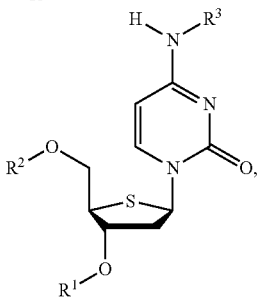
[0441] It is understood that the disclosed kits can be prepared from the disclosed compounds, products, and pharmaceutical compositions. It is also understood that the disclosed kits can be employed in connection with the disclosed methods of using.

[0442] 5. Combination Dosage Forms

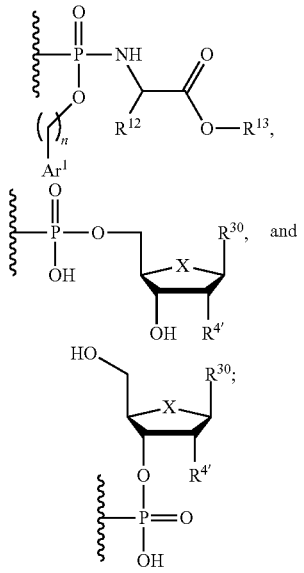
[0443] In one aspect, the invention relates to a combination dosage form comprising at least one compound having a structure represented by a formula selected from:



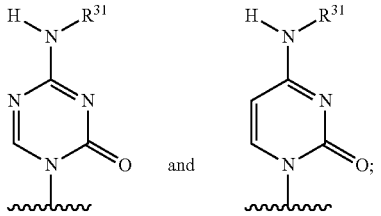
and



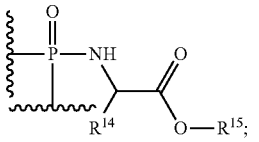
wherein each of R^1 and R^2 is independently selected from hydrogen, —C(O)R^{10}, —P(O)(OR^{11})$_2$, —P(O)(OH)OP(O)(OH)OP(O)(OH)$_2$, and a structure represented by a formula selected from:



provided that one of R^1 and R^2 is hydrogen; wherein n is selected from 0, 1, and 2; wherein X, when present, is selected from O and S; wherein R^{10}, when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and —CH(NH_2)R^{20}; wherein R^{20}, when present, is selected from hydrogen, methyl, isopropyl, isobutyl, sec-butyl, —$(CH_2)_3NHC(NH)NH_2$, —$(CH_2)_4NH_2$, —CH_2CO_2H, —$(CH_2)_2CO_2H$, —CH_2OH, —$CH(OH)CH_3$, —$CH_2C(O)NH_2$, —$(CH_2)_2C(O)NH_2$, —CH_2SH, —$(CH_2)_2SCH_3$, —CH_2SeH, —$CH_2C_6H_5$, and —CH_2Cy^1; wherein Cy^1, when present, is selected from monocylic aryl, para-hydroxy monocyclic aryl, 4-imidazolyl, and 3-indolyl; wherein each occurrence of R^{11}, when present, is independently selected from hydrogen, —(C1-C10 alkyl)CO_2(C1-C10 alkyl), —(C1-C10 alkoxy)CO_2(C1-C10 alkyl), —(C1-C10 alkyl)CO_2(C1-C10 alkylthio), —(C1-C10 alkyl)-S—S—(C1-C10 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and —OH; wherein Ar^2, when present, is selected from aryl and heteroaryl substituted with 1 or 2 groups independently selected from C1-C10 alkyl and nitro; wherein R^{12}, when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylamino, —(C1-C8)C(O)NH_2, aryl, and —(CH_2)aryl; wherein R^{13}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar^3; wherein Ar^3, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino; wherein Ar^1, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino; wherein R^{30}, when present, is a structure selected from:



wherein R^{31}, when present, is selected from hydrogen, —C(O)(C1-C30 alkyl), and —C(O)(C2-C30 alkenyl); or wherein each of R^1 and R^2 together comprise a structure represented by a formula:



wherein R^{14}, when present, is C1-C8 alkyl; wherein R^{15}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and aryl substituted with 0 or 1 C1-C10 alkyl groups; wherein R^3 is selected from hydrogen, —C(O)(C1-C30 alkyl), and —C(O)(C2-C30 alkenyl); wherein each of R^4 and $R^{4'}$, when present, is independently selected from hydrogen, fluoro, —CN, C2-C4 alkenyl, C2-C4 alkynyl, C1-C4 haloalkyl, and —OR^{16}; and wherein R^{16}, when present, is selected from hydrogen, methyl, and —C(O)R^{16}, provided that R^1, R^2, and R^3 are not simultaneously hydrogen, or a pharmaceutically acceptable salt thereof, and one or more of: (a) at least one agent associated with the treatment of a disorder of uncontrolled cellular proliferation; (b) instructions for administering the compound in connection with treating a disorder of uncontrolled cellular proliferation; and (c) instructions for treating a disorder of uncontrolled cellular proliferation.

[0444] In a further aspect, the disorder of uncontrolled cellular proliferation is a cancer. In a still further aspect, the cancer is selected from a sarcoma, a carcinoma, a hematological cancer, a solid tumor, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanoma, glioma, leukemia, lymphoma, chronic myeloproliferative disorder, myelodysplastic syndrome, myeloproliferative neoplasm, and plasma cell neoplasm (myeloma). In yet a further aspect, the cancer is selected from a leukemia, colorectal cancer, pancreatic cancer, ovarian cancer, non-small cell lung carcinoma, and breast cancer. In an even further aspect, the cancer is a liver cancer. In a still further aspect, the liver cancer is selected from hepatocellular carcinoma, cholangiocarcinoma, and biliary tract cancer. In yet a further aspect, the liver cancer is a metastasis originated from another cancer.

[0445] In a further aspect, the at least one agent is a chemotherapeutic agent. In yet a further aspect, the chemotherapeutic agent is selected from an alkylating agent, an

antimetabolite agent, an antineoplastic antibiotic agent, a mitotic inhibitor agent, and a mTor inhibitor agent.

[0446] In a further aspect, the antineoplastic antibiotic agent is selected from doxorubicin, mitoxantrone, bleomycin, daunorubicin, dactinomycin, epirubicin, idarubicin, plicamycin, mitomycin, pentostatin, and valrubicin, or a pharmaceutically acceptable salt thereof.

[0447] In a further aspect, the antimetabolite agent is selected from gemcitabine, 5-fluorouracil, capecitabine, hydroxyurea, mercaptopurine, pemetrexed, fludarabine, nelarabine, cladribine, clofarabine, cytarabine, decitabine, pralatrexate, floxuridine, methotrexate, and thioguanine, or a pharmaceutically acceptable salt thereof.

[0448] In a further aspect, the alkylating agent is selected from carboplatin, cisplatin, cyclophosphamide, chlorambucil, melphalan, carmustine, busulfan, lomustine, dacarbazine, oxaliplatin, ifosfamide, mechlorethamine, temozolomide, thiotepa, bendamustine, and streptozocin, or a pharmaceutically acceptable salt thereof.

[0449] In a further aspect, the mitotic inhibitor agent is selected from irinotecan, topotecan, rubitecan, cabazitaxel, docetaxel, paclitaxel, etopside, vincristine, ixabepilone, vinorelbine, vinblastine, and teniposide, or a pharmaceutically acceptable salt thereof.

[0450] In a further aspect, the mTor inhibitor agent is selected from everolimus, siroliumus, and temsirolimus, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[0451] In a further aspect, the at least one compound and the at least one agent associated with the treatment of a disorder of uncontrolled cellular proliferation are co-formulated. In a further aspect, the at least one compound and the at least one agent associated with the treatment of a disorder of uncontrolled cellular proliferation are co-packaged.

[0452] In a further aspect, the compound and the agent associated with the treatment of a disorder of uncontrolled cellular proliferation are administered sequentially. In a still further aspect, the compound and the agent associated with the treatment of a disorder of uncontrolled cellular proliferation are administered simultaneously.

[0453] The combination dosage forms can also comprise compounds and/or products co-packaged, co-formulated, and/or co-delivered with other components. For example, a drug manufacturer, a drug reseller, a physician, a compounding shop, or a pharmacist can provide a combination dosage form comprising a disclosed compound and/or product and another component for delivery to a patient.

[0454] It is understood that the disclosed combination dosage forms can be prepared from the disclosed compounds, products, and pharmaceutical compositions. It is also understood that the disclosed combination dosage forms can be employed in connection with the disclosed methods of using.

[0455] The foregoing description illustrates and describes the disclosure. Additionally, the disclosure shows and describes only the preferred embodiments but, as mentioned above, it is to be understood that it is capable to use in various other combinations, modifications, and environments and is capable of changes or modifications within the scope of the invention concepts as expressed herein, commensurate with the above teachings and/or the skill or knowledge of the relevant art. The embodiments described herein above are further intended to explain best modes known by applicant and to enable others skilled in the art to utilize the disclosure in such, or other, embodiments and with the various modifications required by the particular applications or uses thereof. Accordingly, the description is not intended to limit the invention to the form disclosed herein. Also, it is intended to the appended claims be construed to include alternative embodiments.

[0456] All publications and patent applications cited in this specification are herein incorporated by reference, and for any and all purposes, as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. In the event of an inconsistency between the present disclosure and any publications or patent application incorporated herein by reference, the present disclosure controls.

F. Examples

[0457] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (e.g., amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in ° C. or is at ambient temperature, and pressure is at or near atmospheric.

[0458] The Examples are provided herein to illustrate the invention, and should not be construed as limiting the invention in any way. Examples are provided herein to illustrate the invention and should not be construed as limiting the invention in any way.

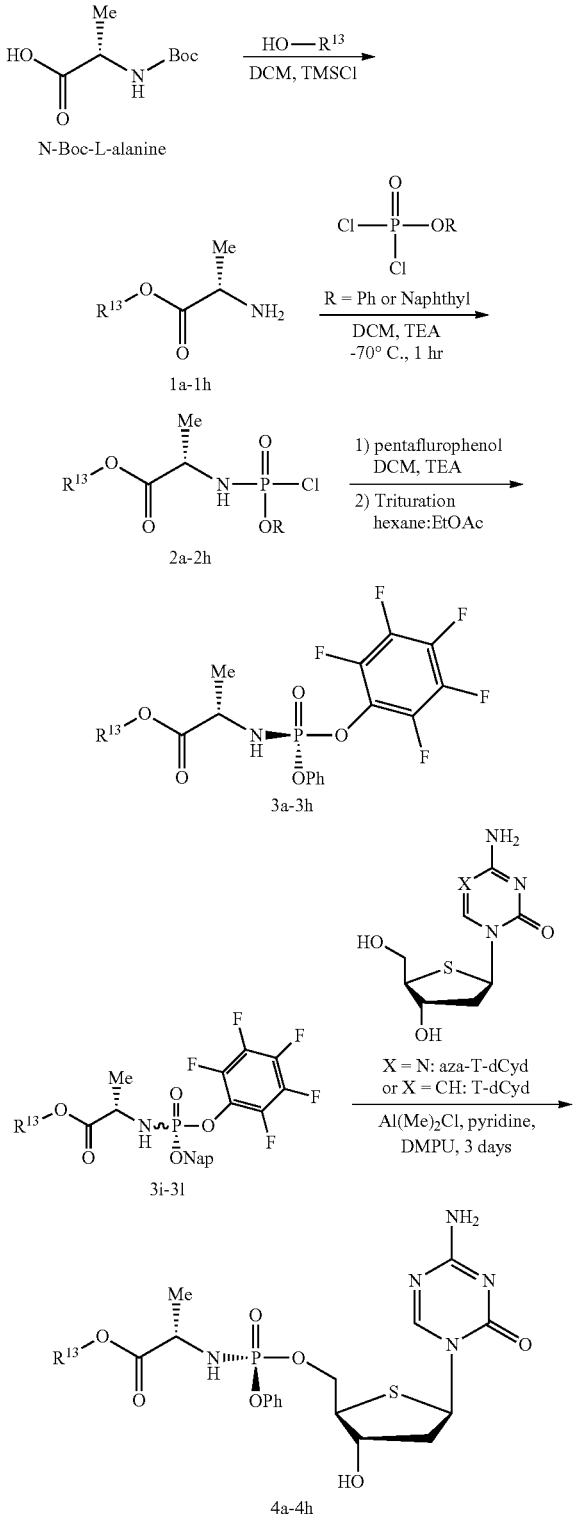
[0459] 1. Chemistry Experimentals

a. General Experimental

[0460] All reactions were carried out in an oven- or flame-dried glassware under argon atmosphere using standard gas-tight syringe, cannula, and septa. The reaction temperatures were measured externally. Stirring was achieved with oven dried magnetic bars. All the reactions were done in anhydrous solvents (DMF, THF, CH_2Cl_2, 1,4-Dioxane, 1-Butanol, $CHCl_3$, DME, pyridine, DMPU) purchased from Sigma-Aldrich. Microwave reactions were performed in CEM discover Labmate System with Intelligent Technology for Focused Microwave Synthesizer (Explorer 48). All commercially purchased reagents were used without purification. The reactions were monitored by thin-layer chromatography (TLC) on a pre-coated silica gel (60 F254) glass plates from EMD Millipore and visualized using UV light (254 nm). Purification of the compounds was performed on Teledyne-ISCO Combiflash Rf 200 purification system or on chiral Supercritical Fluid Chromatography (SFC) using methanol as a mobile phase. Used Redisep Rf® normal phase silica gel columns 230-400 mesh. Proton NMR spectra were recorded on a Varian Unity 400 NMR spectrometer operating at 400 MHz calibrated to the solvent peak and TMS peak. The chemical formula and Exact Mass for target compounds were determined from the (M+H)+ by high resolution mass spectroscopy using an Agilent 6210 Electrospray Time of Flight.

b. General Procedure for the Synthesis of 4'-thio-Nucleotide Analogs

[0461]



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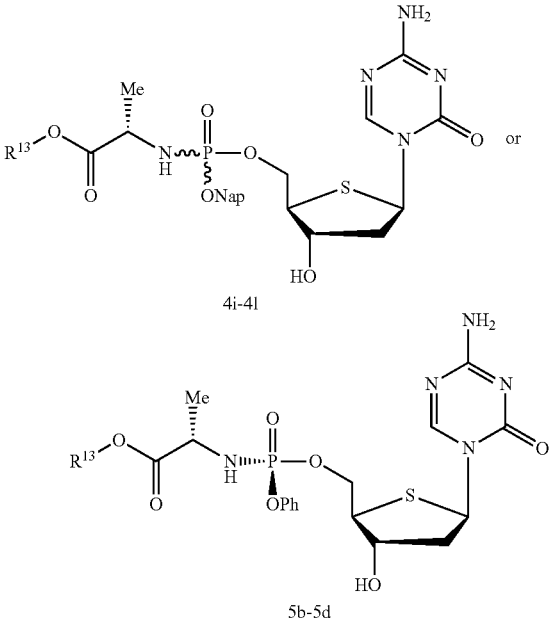
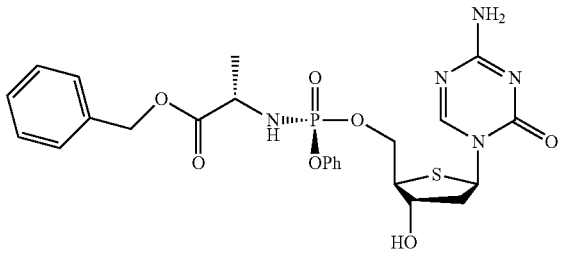


c. Synthesis of Benzyl ((S)-(((2R,3S,5R)-5-(4-amino-2-oxo-1,3,5-triazin-1(2H)-yl)-3-hydroxytetrahydrothiophen-2-yl)methoxy)(phenoxy)phosphoryl)-L-alaninate (4a)

[0462]



I. Preparation of Intermediate Benzyl (chloro(phenoxy)phosphoryl)-L-alaninate (2A)

[0463] To a mixture of L-alanine benzyl ester hydrochloride 1a (2.00 g, 9.27 mmoles, 1.0 Eq.) and methylene chloride (20 mL) was added phenyl dichlorophosphate (1.52 mL, 10.2 mmoles, 1.1 Eq.). The mixture was cooled to −70° C. and then a solution of triethylamine (2.71 mL, 19.5 mmoles, 2.1 Eq.) in methylene chloride (10 mL) was added dropwise at −65° C. Upon completion of addition, the reaction mixture was stirred for 1 hr at −70° C., warmed to 20° C., and then stirred for 2 hrs under argon. The reaction mixture was concentrated in vacou to afford a crude solid, which was triturated in methyl t-butylether (50 mL) for 18 hrs at 20° C. under argon. The mixture was filtered by vacuum filtration to remove triethylamine hydrochloride, which was rinsed with methyl t-butylether (10 mL). The filtrate was concentrated in vacou to afford 3.55 g of intermediate 2a as a light yellow oil, which was used as is without further purification.

ii. Preparation of Benzyl ((S)-(perfluorophenoxy)(phenoxy)phosphoryl)-L-alaninate (3A)

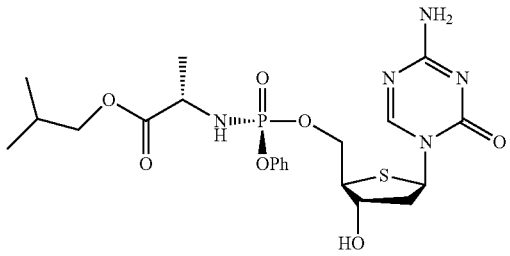
[0464] A solution of intermediate 2a (3.55 g, 10.04 mmoles, 1.0 Eq.) in methylene chloride (20 mL) was cooled to −10° C. and then a solution of pentafluorophenol (2.03 g, 11.04 mmoles, 1.1 Eq.) and triethylamine (1.54 mL, 1.1 Eq.) in methylene chloride (10 mL) was added dropwise at −5° C. Upon completion of addition, the reaction mixture was stirred at 0 to −10° C. for 2 hrs and then for 18 hrs as it warmed to 20° C. under argon. The reaction mixture was concentrated in vacou to give a white solid, which was suspended in ethyl acetate (200 mL) and then triturated for 30 min at 20° C. The mixture was filtered to remove triethyl amine hydrochloride. The filtrate was washed with water (100 mL), 10% Na_2CO_3 (2×100 mL), followed by brine (100 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and then the filtrate was concentrated in vacou to afford 5.39 g of an off-white solid. Purification by trituration in 20% ethyl acetate in hexane (50 mL) at 20° C. for 3 days provided 2.33 g (50% over two steps) of 3a as a single diastereomer. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.48-7.15 (m, 10H), 6.96 (dd, J=14.1, 9.9 Hz, 1H), 5.12 (s, 2H), 4.15-4.00 (m, 1H), 1.33 (dd, J=7.1, 1.3 Hz, 3H); ^{31}P NMR δ_p 0.24; LCMS: m/z 502 (M+H)+.

iii. Preparation of 4a

[0465] To a solution of 5-aza-4'-Thio-2'-deoxycytidine (aza-T-dCyd) (100 mg), DMPU (247 μL, 5 Eq.) and 3a (246 mg, 1.2 Eq.) in 1.2 mL of pyridine was added 0.22 mL of a 1M solution of $Al(Me)_2Cl$ (0.5 Eq.) at 0° C. The slurry mixture was allowed to warm to room temperature over 10 min. and the reaction mixture was stirred at room temperature for 3 days under argon. After solvent removal, the obtained crude was first chromatographed using DCM: MeOH (9:1) as eluent and then purified via SFC to afford 4a in 23% yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.56 (s, 1H), 7.58-7.52 (m, 2H), 7.40-7.26 (m, 7H), 7.24-7.11 (m, 3H), 6.13-6.03 (m, 2H), 5.40 (s, 1H), 5.09 (d, J=2.5 Hz, 2H), 4.34 (d, J=3.8 Hz, 1H), 4.25 (dd, J=10.6, 7.2 Hz, 1H), 4.08-3.83 (m, 2H), 3.49-3.41 (m, 1H), 2.37 (ddd, J=12.7, 8.1, 4.0 Hz, 1H), 2.23 (ddd, J=13.4, 8.6, 5.0 Hz, 1H), 1.29-1.20 (m, 3H); ^{31}P NMR δ_p 3.17; HR-MS: (M+H) calculated for $C_{24}H_{28}N_5O_7PS.H$ was 562.1520; found 562.1509; HPLC purity=94 (% of AUC), t_R=6.7 minutes.

d. Synthesis of Isobutyl ((S)-(((2R,3S,5R)-5-(4-amino-2-oxo-1,3,5-triazin-1(2H)-yl)-3-hydroxytetrahydrothiophen-2-yl)methoxy)(phenoxy)phosphoryl)-L-alaninate (4b)

[0466]



i. Preparation of L-alanine 2-methyl-1-propylester hydrochloride (1b)

[0467] To a solution of N-Boc-L-alanine (3.00 g, 15.9 mmoles, 1.0 Eq.) in 2-methyl-1-propanol (100 mL, 69.0 Eq.) was added trimethylsilylchloride (10.0 mL, 79.28 mmoles, 5.0 Eq.). The reaction mixture was stirred at 20° C. for 18 hrs under argon. The reaction mixture was concentrated under vacou to afford a residue, which was triturated in anhydrous diethyl ether (50 mL) for 1 hr. The mixture was filtered by vacuum filtration to collect a solid, which was rinsed with diethyl ether (20 mL) and then dried to provide 2.66 g (92%) of intermediate 1b as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.61 (s, 3H), 4.09 (q, J=7.2 Hz, 1H), 4.04-3.89 (m, 2H), 1.94 (dh, J=13.4, 6.6 Hz, 1H), 1.45 (d, J=7.2 Hz, 3H), 0.93 (dd, J=6.7, 0.7 Hz, 6H).

11. Preparation of Isobutyl (chloro(phenoxy)phosphoryl)-L-alaninate (2b)

[0468] Intermediate 2b was prepared from intermediate 1b (L-alanine-2-methyl-1-propylester hydrochloride) (2.0 g, 11.0 mmoles, 1.0 Eq.) and phenyl dichlorophosphate (1.81 mL, 12.1 mmoles, 1.1 Eq.) by the procedure described for the preparation of intermediate 2a to provide 3.83 g of a colorless oil.

iii. Preparation of Isobutyl ((S)-(perfluorophenoxy)(phenoxy)phosphoryl)-L-alaninate (3b)

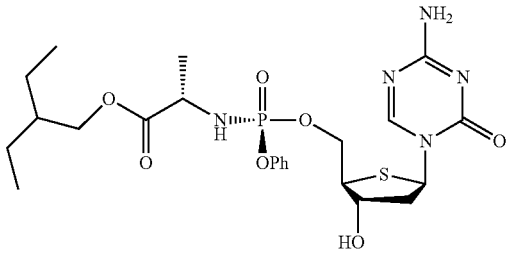
[0469] Compound 3b was prepared from 2b (3.83 g, 12.0 mmoles, 1.0 Eq.) and pentafluorophenol (2.43 g, 13.2 mmoles, 1.1 Eq.) according to the procedure described for the preparation of 3a to afford a solid. Trituration in a mixture of 20% ethyl acetate in hexane (50 mL) provided 1.43 g of 3b as a single diastereomer. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.43 (dd, J=8.5, 7.3 Hz, 2H), 7.32-7.18 (m, 3H), 6.91 (dd, J=14.2, 9.9 Hz, 1H), 4.11-3.95 (m, 1H), 3.84 (d, J=6.5 Hz, 2H), 1.86 (dh, J=13.3, 6.7 Hz, 1H) 1.32 (dd, J=7.1, 1.2 Hz, 3H), 0.88 (d, J=6.7 Hz, 6H); ^{31}P NMR δ_p 0.29; LCMS: m/z 468 (M+H)+.

iv. Preparation of 4b

[0470] Compound 4b was prepared from aza-T-dCyd (100 mg) and 3b (230 mg, 1.2 Eq.) according to the procedure described for the preparation of 4a. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 7.55 (s, 2H), 7.36 (dd, J=8.5, 7.2 Hz, 2H), 7.26-7.09 (m, 3H), 6.15-5.88 (m, 2H), 5.39 (d, J=3.7 Hz, 1H), 4.35 (t, J=3.7 Hz, 1H), 4.27 (dt, J=10.7, 7.2 Hz, 1H), 4.10-3.97 (m, 1H), 3.92-3.72 (m, 3H), 3.44 (td, J=6.9, 2.8 Hz, 1H), 2.38 (ddd, J=12.8, 8.4, 4.0 Hz, 1H), 2.23 (dt, J=13.2, 5.7 Hz, 1H), 1.84 (hept, J=6.7 Hz, 1H), 1.27-1.22 (m, 3H), 0.86 (d, J=6.8 Hz, 6H); ^{31}P NMR δ_p 3.17; HR-MS: (M+H) calculated for $C_{21}H_{30}N_5O_7PS.H$ was 528.1676; found 528.1669; HPLC purity=97 (% of AUC), t_R=6.65 minutes.

e. Synthesis of 2-ethylbutyl ((S)-(((2R,3S,5R)-5-(4-amino-2-oxo-1,3,5-triazin-1(2H)-yl)-3-hydroxytetrahydrothiophen-2-yl)methoxy)(phenoxy)phosphoryl)-L-alaninate (4c)

[0471]



i. Preparation of 2-ethylbutyl L-alaninate Hydrochloride (1c)

[0472] Intermediate 1c was prepared from N-Boc-L-alanine (6.00 g, 31.7 mmoles, 1.0 Eq.) and 2-ethyl-1-butanol (100 mL, 812 mmoles, 26.0 Eq.) according to the procedure described for the preparation of intermediate 1a to afford 5.19 g (78%) of a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.63 (s, 3H), 4.19-3.98 (m, 3H), 1.53 (h, 1H), 1.44 (d, J=7.2 Hz, 3H), 1.40-1.29 (m, 4H), 0.93-0.82 (m, 6H).

ii. Preparation of 2-ethylbutyl (chloro(phenoxy)phosphoryl)-L-alaninate (2c)

[0473] Intermediate 2c was prepared from intermediate 1c (2.00 g, 9.54 mmoles, 1.0 Eq.) and phenyl dichlorophosphate (1.56 mL, 10.5 mmoles, 1.1 Eq.) according to the procedure described for the preparation of intermediate 2a to afford 3.58 g of a yellow oil.

iii. Preparation of Isobutyl ((S)-(perfluorophenoxy)(phenoxy)phosphoryl)-L-Alaninate (3c)

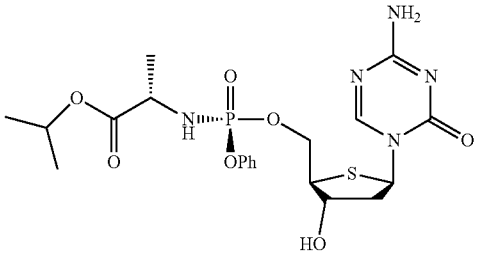
[0474] Compound 3c was prepared from intermediate 2c (3.58 g, 10.29 mmoles, 1.0 Eq) and pentafluorophenol (2.08 g, 11.3 mmoles, 1.1 Eq.) according to the procedure described for the preparation of 3a. Trituration in 5% ethyl acetate in hexane (25 mL) provided 1.70 g as a white cotton-like solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.48-7.38 (m, 2H), 7.30-7.19 (m, 3H), 6.90 (dd, J=14.2, 9.9 Hz, 1H), 4.12-3.88 (m, 3H), 1.46 (h, J=6.1 Hz, 1H), 1.37-1.22 (m, 7H), 0.84 (t, J=7.5 Hz, 6H); ^{31}P NMR δ_p 0.26; LCMS: m/z 496 $(M+H)^+$.

iv. Preparation of 4c

[0475] Compound 4c was prepared from aza-T-dCyd (100 mg) and 3c (243 mg, 1.2 Eq.) according to the procedure described for the preparation of 4a. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 7.55 (s, 2H), 7.40-7.31 (m, 2H), 7.24-7.12 (m, 3H), 6.14-6.05 (m, 1H), 6.02 (dd, J=13.1, 10.1 Hz, 1H), 5.39 (d, J=3.8 Hz, 1H), 4.39-4.32 (m, 1H), 4.27 (dt, J=10.7, 7.2 Hz, 1H), 4.09-3.76 (m, 4H), 3.44 (m, 1H), 2.38 (ddd, J=12.7, 8.3, 4.0 Hz, 1H), 2.28-2.17 (m, 1H), 1.45 (p, J=6.2 Hz, 1H), 1.23 (m, 7H), 0.89-0.77 (m, 6H); ^{31}P NMR δ_p 3.17; HR-MS: (M+H) calculated for $C_{23}H_{34}N_5O_7PS.H$ was 556.1989 found 556.1983; HPLC purity=99 (% of AUC), t_R=7.62 minutes.

f. Synthesis of Isopropyl ((S)-(((2R,3S,5R)-5-(4-amino-2-oxo-1,3,5-triazin-1(2H)-yl)-3-hydroxytetrahydrothiophen-2-yl)methoxy)(phenoxy)phosphoryl)-L-alaninate (4d)

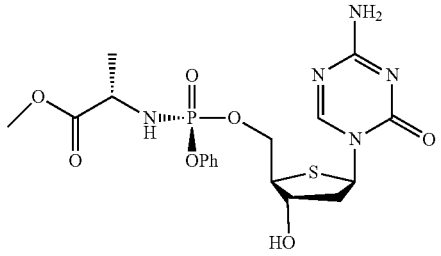
[0476]



[0477] Compound 4d was prepared from aza-T-dCyd (100 mg) and 3d (222 mg, 1.2 Eq.), which was purchased as (S,S_P) diastereisomer, according to the procedure described for the preparation of 4a. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 7.55 (s, 2H), 7.41-7.31 (m, 2H), 7.25-7.09 (m, 3H), 6.09 (dd, J=8.3, 6.5 Hz, 1H), 5.99 (dd, J=13.2, 10.1 Hz, 1H), 5.41 (s, 1H), 4.86 (hept, J=6.2 Hz, 1H), 4.36 (s, 1H), 4.26 (ddd, J=10.7, 7.8, 6.5 Hz, 1H), 4.11-3.99 (m, 1H), 3.77 (tq, J=10.3, 7.1 Hz, 1H), 3.49-3.33 (m, 1H), 3.15 (d, J=5.2 Hz, 1H), 2.39 (ddd, J=12.8, 8.4, 4.0 Hz, 1H), 2.23 (ddd, J=13.2, 6.5, 4.0 Hz, 1H), 1.18 (ddd, J=23.5, 6.7, 2.0 Hz, 9H); ^{31}P NMR δ_p 3.19; HPLC purity=98 (% of AUC), t_R=5.66 minutes.

g. Synthesis of Methyl ((S)-(((2R,3S,5R)-5-(4-amino-2-oxo-1,3,5-triazin-1(2H)-yl)-3-hydroxytetrahydrothiophen-2-yl)-methoxy)(phenoxy)-phosphoryl)-L-alaninate (4E)

[0478]



1. Preparation of Methyl ((S)-chloro(phenoxy)-phosphoryl)-L-alaninate (2e)

[0479] Intermediate 2e was prepared from intermediate (L-alanine-2-methyl-1-methylester hydrochloride) (10.0 g, 71.6 mmoles, 1.0 Eq.) and phenyl dichlorophosphate (11.8 mL, 12.1 mmoles, 1.1 Eq.) by the procedure described for the preparation of intermediate 2a to provide 21.3 g of a yellow oil.

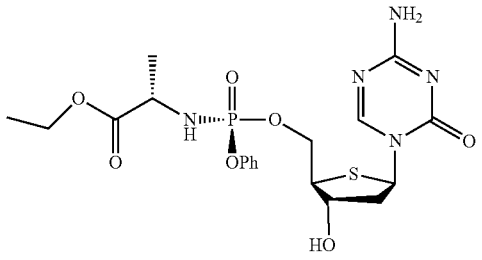
ii. Preparation of Methyl ((S)-(perfluorophenoxy)(phenoxy)phosphoryl)-L-alaninate (3e)

[0480] Compound 3e was prepared from 2e (19.9 g, 71.6 mmoles, 1.0 Eq.) and pentafluorophenol (14.5 g, 78.8 mmoles, 1.1 Eq.) according to the procedure described for the preparation of 3a to afford a solid. Trituration in a mixture of 5% ethyl acetate in hexane (100 mL) provided 4.14 g of 3e as a single diastereomer. The filtrate was purified by flash chromatography (220 g silica column, 100-70% hexane in ethyl acetate, gradient elution) to afford 4.25 g of additional product 3e as a single diastereomer. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.48-7.39 (m, 2H), 7.30-7.21 (m, 3H), 6.91 (dd, J=14.1, 9.9 Hz, 1H), 4.01 (ddq. J=10.9, 9.9, 7.1 Hz, 1H), 3.61 (s, 3H), 1.29 (dd, J=7.1, 1.2 Hz, 3H); ^{31}1)NMR δ_p 0.35; LCMS: m/z 426 $(M+H)^+$.

iii. Preparation of 4e

[0481] Compound 4e was prepared from aza-T-dCyd (100 mg) and 3e (209 mg, 1.2 Eq.) according to the procedure described for the preparation of 4a. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 7.58 (s, 2H), 7.45-7.35 (m, 2H), 7.28-7.15 (m, 3H), 6.17-6.01 (m, 2H), 5.43 (d, J=3.9 Hz, 1H), 4.43-4.36 (m, 1H), 4.30 (ddd, J=10.7, 7.7, 6.6 Hz, 1H), 4.08 (dt, J=10.7, 6.6 Hz, 1H), 3.94-3.81 (m, 1H), 3.62 (s, 3H), 3.48 (ddd, J=7.4, 6.2, 3.0 Hz, 1H), 2.42 (ddd, J=12.7, 8.3, 4.0 Hz, 1H), 2.27 (ddd, J=13.3, 6.6, 4.2 Hz, 1H), 1.26 (dd, J=7.2, 1.0 Hz, 3H); ^{31}P NMR δ_p 3.11; HR-MS: (M+H) calculated for $C_{18}H_{24}N_5O_7PS.H$ was 486.12023; found 485.1131; HPLC purity=98 (% of AUC), t_R=8.68 minutes.

[0482] h. Synthesis of Ethyl ((S)-(((2R,3S,5R)-5-(4-amino-2-oxo-1,3,5-triazin-1(2H)-yl)-3-hydroxytetrahydrothiophen-2-yl)-methoxy)(phenoxy)-phosphoryl)-L-alaninate (41)



1. Preparation of Ethyl ((S)-chloro(phenoxy)-phosphoryl)-L-alaninate (2f)

[0483] Intermediate 2f was prepared from intermediate (L-alanine-2-methyl-1-ethylester hydrochloride) (6.50 g, 42.3 mmoles, 1.0 Eq.) and phenyl dichlorophosphate (6.94 mL, 46.6 mmoles, 1.1 Eq.) by the procedure described for the preparation of intermediate aa to provide 14.0 g of 2f a colorless oil.

ii. Preparation of Ethyl ((S)-perfluorophenoxy)-(phenoxy)phosphoryl)-L-alaninate (3f)

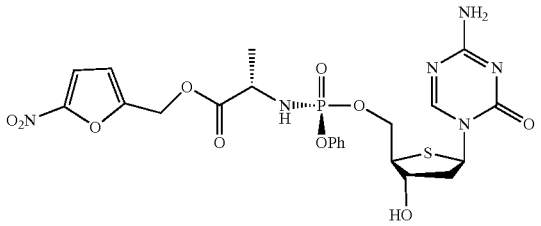
[0484] Compound 3f was prepared from 2f (19.9 g, 71.6 mmoles, 1.0 Eq.) and pentafluorophenol (12.4 g, 42.3 mmoles, 1.1 Eq.) according to the procedure described for the preparation of 3a to afford a solid. Trituration in a mixture of 5% ethyl acetate in hexane (500 mL) provided 5.54 g of 3f as a single diastereomer. The filtrate was purified by flash chromatography (220 g silica column, 100-80% hexane in ethyl acetate, gradient elution) to afford 2.74 g of additional product 3f as a single diastereomer. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.48-7.38 (m, 2H), 7.26 (dddt, J=9.8, 7.7, 2.3, 1.1 Hz, 3H), 6.89 (ddd, J=13.9, 9.9, 6.4 Hz, 1H), 4.12-4.04 (m, 2H), 4.04-3.92 (m, 1H), 1.30 (ddd, J=7.1, 5.0, 1.2 Hz, 3H), 1.17 (t, J=7.1 Hz, 3H); ^{31}P NMR δ_p 0.33; LCMS: m/z 440 $(M+H)^+$.

iii. Preparation of 4f

[0485] Compound 4f was prepared from aza-T-dCyd (100 mg) and 3f (216 mg, 1.2 Eq.) according to the procedure described for the preparation of 4a. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 7.58 (s, 2H), 7.44-7.35 (m, 2H), 7.28-7.15 (m, 3H), 6.13 (dd, J=8.3, 6.5 Hz, 1H), 6.05 (dd, J=13.2, 10.0 Hz, 1H), 5.43 (d, J=3.9 Hz, 1H), 4.39 (p, J=3.8 Hz, 1H), 4.30 (ddd, J=10.7, 7.7, 6.5 Hz, 1H), 4.08 (qd, J=7.1, 1.0 Hz, 3H), 3.91-3.79 (m, 1H), 3.51-3.44 (m, 1H), 2.42 (ddd, J=12.7, 8.4, 4.1 Hz, 1H), 2.26 (ddd, J=13.2, 6.5, 4.0 Hz, 1H), 1.26 (dd, J=7.1, 1.0 Hz, 3H), 1.18 (t, J=7.1 Hz, 3H); ^{31}P NMR δ_p 3.15; HR-MS: (M+H) calculated for $C_{19}H_{26}N_5O_7PS.H$ was 500.13574; found 499.1286; HPLC purity=95 (% of AUC), t_R=9.41 minutes.

1. Synthesis of (5-nitrofuran-2-yl)methyl ((S)-(((2R,3S,5R)-5-(4-amino-2-oxo-1,3,5-triazin-1(2H)-yl)-3-hydroxytetrahydro-thiophen-2-yl)-methoxy)(phenoxy)-phosphoryl)-L-alaninate (4g)

[0486]



i. Preparation of (5-nitrofuran-2-yl)methyl L-alaninate (1g)

[0487] Intermediate 1g was prepared from N-Boc-L-alanine (10.0 g, 52.85 mmoles, 1.0 Eq.) and hydroxy-[5-(hydroxymethyl)-2-furyl]-oxo-ammonium (264.26 mmoles, 5.0 Eq) following the procedure described for the preparation of intermediate 1a to provide 8 g (60.15%) of intermediate 1g as a white solid. 1H NMR (400 MHz, DMSO-d6) δ 8.63 (s, 3H), 7.69 (d, J=3.7 Hz, 1H), 7.13-6.87 (m, 1H), 5.33 (s, 2H), 4.14 (q, J=7.1 Hz, 1H), 1.41 (d, J=7.2 Hz, 3H).

ii. Preparation of (5-nitrofuran-2-yl)methyl ((S)-(perfluorophenoxy)-(phenoxy)phosphoryl)-L-alaninate (3g)

[0488] Intermediate 3g was prepared from intermediate (1g) (5-nitrofuran-2-yl)methyl L-alaninate following the procedure described for the preparation of intermediate 3f to afford 8 g (64%) of 3g as a single diastereomer. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.62 (d, J=3.8 Hz, 1H), 7.37 (t, J=7.9 Hz, 2H), 7.28-7.08 (m, 3H), 6.98 (dd, J=14.0, 9.8 Hz,

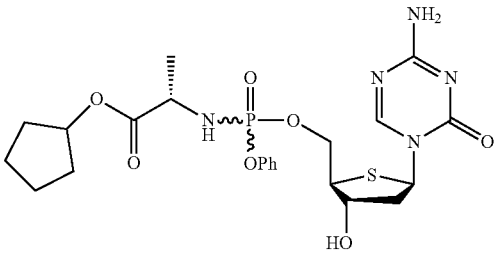
1H), 6.88 (d, J=3.8 Hz, 1H), 5.19 (d, J=1.9 Hz, 2H), 4.12-3.96 (m, 1H), 1.30 (dd, J=7.2, 1.3 Hz, 3H).

iii. Preparation of 4g

[0489] Compound 4g was prepared from aza-T-dCyd (100 mg) and 3g (216 mg, 1.2 Eq.) according to the procedure described for the preparation of 4a. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.55 (s, 1H), 7.64 (d, J=3.8 Hz, 1H), 7.54 (d, J=2.7 Hz, 2H), 7.39-7.27 (m, 2H), 7.22-7.08 (m, 3H), 6.95-6.84 (m, 1H), 6.21-6.00 (m, 2H), 5.73 (s, OH), 5.38 (d, J=4.0 Hz, 1H), 5.23-5.16 (m, 2H), 4.34 (p, J=3.9 Hz, 1H), 4.26 (dt, J=10.7, 7.2 Hz, 1H), 4.11-3.85 (m, 3H), 3.42 (ddd, J=9.6, 6.7, 3.0 Hz, 1H), 3.15 (d, J=5.2 Hz, 1H), 2.42-2.30 (m, 1H), 2.22 (ddd, J=13.2, 6.4, 4.3 Hz, 1H), 1.25 (dt, J=7.1, 1.6 Hz, 3H); ^{31}P NMR (162 MHz, DMSO-d6) δ 3.093; HR-MS: (M+H) calculated for $C_{22}H_{25}N_6O_{10}PS.H$ was 597.1163; found 597.11; HPLC purity=95.3 (% of AUC).

j. Synthesis of Cyclopentyl ((((2R,3S,5R)-5-(4-amino-2-oxo-1,3,5-triazin-1(2H)-yl)-3-hydroxytetrahydrothiophen-2-yl)methoxy)(phenoxy)phosphoryl)-L-alaninate (4h)

[0490]



i. Preparation of Ethyl ((S)-chloro(phenoxy)-phosphoryl)-L-alaninate (1h)

[0491] Intermediate 1h was prepared from N-Boc-L-alanine (10.0 g, 52.85 mmoles, 1.0 Eq.) and cyclopentanol (264.26 mmoles, 5.0 Eq) following the procedure described for the preparation of intermediate 1a to provide 7.0 g (84%) of intermediate 1h as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 3H), 5.15 (tt, J=5.9, 2.3 Hz, 1H), 4.31 (s, 3H), 3.97 (q, J=7.2 Hz, 1H), 1.83 (ddddd, J=12.1, 8.1, 6.0, 4.1, 1.7 Hz, 2H), 1.73-1.48 (m, 10H), 1.48-1.39 (m, 7H), 1.39-1.34 (m, 3H).

ii. Preparation of Ethyl ((S)-(perfluorophenoxy)-(phenoxy)phosphoryl)-L-alaninate (3h)

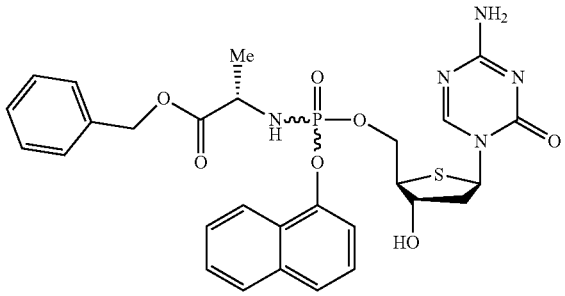
[0492] Intermediate 3h was prepared from intermediate (1h) cyclopentyl 2-aminopropanoate following the procedure described for the preparation of intermediate 3a to afford a solid. The solid was stiffed in EtOAc and warmed slightly to get everything into solution, then allowed to cool and a solid formed. The solid was filtered and dried to provide 15 grams (44%) of 3h as a single diastereomer. ^{31}P NMR (162 MHz, DMSO-d6) δ 0.28. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.39 (t, J=7.9 Hz, 2H), 7.29-7.09 (m, 3H), 6.83 (dd, J=14.2, 9.9 Hz, 1H), 5.02 (tt, J=5.4, 2.5 Hz, 1H), 3.90 (tq, J=10.3, 7.1 Hz, 1H), 1.90-1.69 (m, 2H), 1.66-1.41 (m, 6H), 1.24 (dd, J=7.2, 1.2 Hz, 3H).

iii. Preparation of 4h

[0493] Compound 4h was prepared from aza-T-dCyd (100 mg) and 3h (216 mg, 1.2 Eq.) according to the procedure described for the preparation of 4a. Diastereoisomer 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 7.55 (d, J=4.1 Hz, 2H), 7.40-7.29 (m, 2H), 7.24-7.07 (m, 3H), 6.16-6.03 (m, 1H), 5.95 (dd, J=12.8, 10.0 Hz, 1H), 5.42 (d, J=3.8 Hz, 1H), 5.09-4.94 (m, 1H), 4.45-4.33 (m, 1H), 4.33-4.20 (m, 1H), 4.18-4.03 (m, 1H), 3.81-3.67 (m, 1H), 3.58-3.42 (m, 2H), 2.36-2.16 (m, 2H), 1.85-1.68 (m, 2H), 1.67-1.41 (m, 2H), 1.24-1.08 (m, 3H); ^{31}P NMR (162 MHz, DMSO-d6) δ 3.36; HR-MS: (M+H) calculated for $C_{22}H_{30}N_5O_7PS.H$ was 540.16; found 540.16; HPLC purity=97.8 (% of AUC). Diastereoisomer 2: ^{1}H NMR (400 MHz, DMSO-d6) δ 8.56 (d, J=1.3 Hz, 1H), 7.68-7.47 (m, 2H), 7.41-7.28 (m, 2H), 7.25-7.06 (m, 3H), 6.10 (ddd, J=8.5, 6.5, 4.5 Hz, 1H), 5.96 (td, J=12.7, 10.0 Hz, 1H), 5.41 (dd, J=9.1, 3.9 Hz, 1H), 5.08-4.95 (m, 1H), 4.37 (dp, J=11.1, 3.8 Hz, 1H), 4.31-4.22 (m, 1H), 4.16-3.98 (m, 2H), 3.84-3.69 (m, 1H), 3.54-3.38 (m, 1H), 3.18-3.12 (m, 3H), 2.44-2.29 (m, 1H), 2.29-2.17 (m, 1H), 1.76 (s, 1H), 1.65-1.41 (m, 2H), 1.19 (td, J=7.3, 1.0 Hz, 3H); ^{31}P NMR (162 MHz, DMSO-d6) δ 3.21; HR-MS: (M+H) calculated for $C_{22}H_{30}N_5O_7PS.H$ was 540.16; found 540.16; HPLC purity=97.5 (% of AUC).

k. Synthesis of benzyl((((2R,3S,5R)-5-(4-amino-2-oxo-1,3,5-triazin-1(2H)-yl)-3-hydroxytetrahydropthiophen-2-yl)methoxy)(naphthalen-1-yloxy)phosphoryl-L-alaninate (4i)

[0494]



i. Preparation of Benzyl ((naphthalen-1-yloxy)(perfluorophenoxy)phosphoryl)-L-alaninate (3i)

[0495] Intermediate 2i was prepared according to the procedure described for the preparation of 2a. A solution of 2i (5.79 g, 14.3 mmoles, 1.0 Eq.) in methylene chloride (30 mL) was cooled to −5° C. and then a solution of pentafluorophenol (2.90 g, 15.8 mmoles, 1.1 Eq.) and triethylamine (2.20 mL, 15.8 mmoles, 1.1 Eq.) in methylene chloride (10 mL) was added dropwise at −5° C. Upon completion of addition, the reaction mixture was stirred at -5 to −10° C. for 1 hr and then for 18 hrs as it warmed to 20° C. under argon. The reaction mixture was concentrated in vacou to give a white solid, which was suspended in ethyl acetate (200 mL) and then triturated for 30 min at 20° C. The mixture was filtered to remove triethyl amine hydrochloride. The filtrate was washed with water (100 mL), 10% Na_2CO_3 (2×100 mL), followed by brine (100 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and then the filtrate was

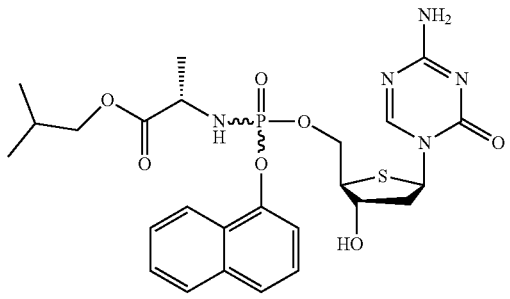
concentrated in vacou to afford 6.79 g of a tan oil. Purification by flash chromatography (silica gel, 99% to 95% dichloromethane in ethyl acetate, gradient elution) provided 830 mg (11%) of 3i as a mixture of two diastereomers. Diastereomer 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18-8.09 (m, 1H), 8.06-7.95 (m, 1H), 7.83 (dd, J=8.2, 1.1 Hz, 1H), 7.68-7.44 (m, 4H), 7.40-7.26 (m, 5H), 7.15 (dd, J=13.5, 9.8 Hz, 1H), 5.13 (s, 2H), 4.25-4.09 (m, 1H), 1.36 (dd, J=7.1, 1.2 Hz, 3H); ^{31}P NMR δ_p0.81; ^{19}F NMR; LCMS: m/z 552 $(M+H)^+$. Diastereomer 2: ^{1}H NMR (400 MHz, DMSO-d6) δ 8.22-8.06 (m, 1H), 8.04-7.95 (m, 1H), 7.83 (dt, J=8.1, 1.1 Hz, 1H), 7.68-7.43 (m, 4H), 7.31 (s, 5H), 7.17 (dd, J=14.0, 9.9 Hz, 1H), 5.12-5.03 (m, 2H), 4.27-4.11 (m, 1H), 1.39 (dd, J=7.2, 1.3 Hz, 3H); ^{31}P NMR δ_p 0.52; ^{19}F NMR; LCMS: m/z 552 $(M+H)^+$.

ii. Preparation of 4i

[0496] Compound 4i was prepared from aza-T-dCyd (100 mg) and 3i (270 mg, 1.2 Eq.) according to the procedure described for the preparation of 4a. Diastereomer 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.15-8.06 (m, 1H), 7.99-7.88 (m, 1H), 7.76-7.65 (m, 1H), 7.59-7.51 (m, 4H), 7.49-7.39 (m, 2H), 7.36-7.26 (m, 5H), 6.26 (dd, J=12.8, 10.0 Hz, 1H), 6.08 (dd, J=8.2, 6.5 Hz, 1H), 5.39 (d, J=3.9 Hz, 1H), 5.07 (d, J=2.0 Hz, 2H), 4.39-4.25 (m, 2H), 4.09 (dt, J=10.6, 6.9 Hz, 1H), 4.03-3.90 (m, 1H), 3.46 (dt, J=7.1, 3.8 Hz, 1H), 2.36 (ddd, J=12.7, 8.3, 4.0 Hz, 1H), 2.21 (ddd, J=13.2, 6.6, 4.2 Hz, 1H), 1.27 (dd, J=7.2, 0.9 Hz, 3H). ^{31}P NMR δ_p 3.63; HR-MS: (M+H) calculated for $C_{28}H_{30}N_5O_7PS.H$ was 612.1675; found 612.1676; HPLC purity=99 (% of AUC), t_R=7.53 minutes. Diastereomer 2: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.15-8.06 (m, 1H), 7.99-7.88 (m, 1H), 7.76-7.65 (m, 1H), 7.59-7.51 (m, 4H), 7.49-7.39 (m, 2H), 7.36-7.26 (m, 5H), 6.26 (dd, J=12.8, 10.0 Hz, 1H), 6.08 (dd, J=8.2, 6.5 Hz, 1H), 5.39 (d, J=3.9 Hz, 1H), 5.07 (d, J=2.0 Hz, 2H), 4.39-4.25 (m, 2H), 4.09 (dt, J=10.6, 6.9 Hz, 1H), 4.03-3.90 (m, 1H), 3.46 (dt, J=7.1, 3.8 Hz, 1H), 2.36 (ddd, J=12.7, 8.3, 4.0 Hz, 1H), 2.21 (ddd, J=13.2, 6.6, 4.2 Hz, 1H), 1.27 (dd, J=7.2, 0.9 Hz, 3H); ^{31}P NMR δ_p 3.69; HR-MS: (M+H) calculated for $C_{28}H_{30}N_5O_7PS.H$ was 612.1675; found 612.1671; HPLC purity=97 (% of AUC), t_R=7.88 minutes.

1. Synthesis of Isobutyl ((((2R,3S,5R)-5-(4-amino-2-oxo-1,3,5-triazin-1(2H)-yl)-3-hydroxytetrahydrothiophen-2-yl)methoxy)(naphthalen-1-yloxy)phosphoryl)-L-alaninate (4j)

[0497]



i. Preparation of Isobutyl ((naphthalen-1-yloxy)(perfluorophenoxy)phosphoryl)-L-alaninate (3j)

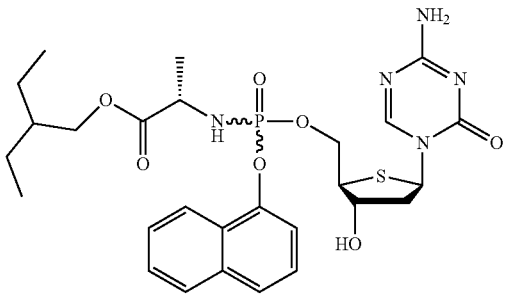
[0498] Compound 3j was prepared as a mixture of two diastereomers from 2j (5.64 g, 15.3 mmoles, 1.0 Eq.) and pentafluorophenol according to the procedure described for the preparation of 3i. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.22-8.07 (m, 1H), 8.05-7.96 (m, 1H), 7.84 (DDD, J=8.1, 2.6, 1.3 Hz, 1H), 7.71-7.46 (m, 4H), 7.11 (ddd, J=15.3, 13.8, 9.9 Hz, 1H), 4.22-4.01 (m, 1H), 3.94-3.68 (m, 2H), 1.82 (dhept, J=11.7, 6.7 Hz, 1H), 1.36 (ddd, J=11.1, 7.1, 1.2 Hz, 3H), 0.94-0.75 (m, 6H); ^{19}F NMR of -153.32 to -154.10 (m, 2F), −159.86 to −160.61 (m, 1F), −163.07 (dtd, J=33.5, 23.2, 3.9 Hz, 2F); ^{31}P NMR δ_p 0.93, 0.48; LCMS: m/z 518 $(M+H)^+$.

ii. Preparation of 4j

[0499] Compound 4j was prepared from aza-T-dCyd (100 mg) and 3j (254 mg, 1.2 Eq.) according to the procedure described for the preparation of 4a. Diastereomer 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.13-8.03 (m, 1H), 7.97-7.86 (m, 1H), 7.72 (dd, J=5.7, 3.7 Hz, 1H), 7.59-7.42 (m, 6H), 6.19 (dd, J=12.9, 10.0 Hz, 1H), 6.09 (dd, J=8.2, 6.5 Hz, 1H), 5.42 (d, J=4.0 Hz, 1H), 4.48-4.26 (m, 2H), 4.19 (dt, J=10.7, 6.4 Hz, 1H), 3.91 (ddt, J=17.1, 9.9, 7.1 Hz, 1H), 3.80-3.62 (m, 2H), 3.52 (td, J=7.1, 3.0 Hz, 1H), 2.38-2.11 (m, 2H), 1.77 (dp, J=13.3, 6.6 Hz, 1H), 1.25 (dd, J=7.3, 1.1 Hz, 3H), 0.80 (d, J=6.7 Hz, 6H); ^{31}P NMR δ_p 3.60; HR-MS: (M+H) calculated for $C_{25}H_{32}N_5O_7PS.H$ was 578.1833; found 578.1832; HPLC purity=97 (% of AUC), t_R=7.55 minutes. Diastereomer 2: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.14-8.03 (m, 1H), 7.97-7.86 (m, 1H), 7.73 (dd, J=5.4, 3.9 Hz, 1H), 7.63-7.39 (m, 6H), 6.20 (dd, J=12.8, 10.1 Hz, 1H), 6.09 (dd, J=8.2, 6.5 Hz, 1H), 5.39 (d, J=3.9 Hz, 1H), 4.43-4.26 (m, 2H), 4.10 (dt, J=10.7, 6.8 Hz, 1H), 3.97-3.87 (m, 1H), 3.78 (t, J=6.4 Hz, 2H), 3.48-3.40 (m, 1H), 2.37 (ddd, J=12.7, 8.4, 4.1 Hz, 1H), 2.22 (ddd, J=13.2, 6.6, 4.2 Hz, 1H), 1.79 (dq, J=13.3, 6.7 Hz, 1H), 1.26 (dd, J=7.1, 1.0 Hz, 3H), 0.83 (d, J=6.7 Hz, 6H); ^{31}P NMR δ_p 3.71; HR-MS: (M+H) calculated for $C_{25}H_{32}N_5O_7PS.H$ was 578.1833; found 578.1832; HPLC purity=97 (% of AUC), t_R=7.81 minutes.

m. Synthesis of 2-Ethylbutyl ((((2R,3S,5R)-5-(4-amino-2-oxo-1,3,5-triazin-1(2H)-yl)-3-hydroxytetrahydrothiophen-2-yl)methoxy)(naphthalen-1-yloxy)phosphoryl)-L-alaninate (4k)

[0500]



i. Preparation of 2-ethylbutyl ((naphthalen-1-yloxy)(perfluorophenoxy)phosphoryl)-L-alaninate (3k)

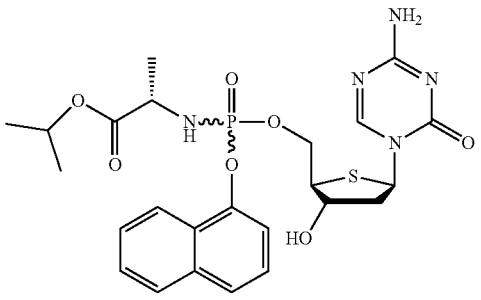
[0501] Compound 4k was prepared as a mixture of two diastereomers from 3k and pentafluorophenol according to the procedure described for the preparation of 3i. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.19-8.07 (m, 1H), 8.00 (dtt, J=5.5, 3.5, 0.60 Hz, 1H), 7.87-7.78 (m, 1H), 7.69-7.47 (m, 4H), 7.10 (ddd, J=16.3, 13.8, 9.9 Hz, 1H), 4.20-3.80 (m, 3H), 1.49-1.20 (m, 7H), 0.83-0.73 (m, 6H); ^{19}F NMR of -153.22 to -154.29 (m, 2F), -160.22 (dtd, J=27.3, 23.4, 3.4 Hz, 1F), -163.08 (dtd, J=38.6, 23.7, 4.0 Hz, 2F); ^{31}I) NMR δ_p 0.91 and 0.45; LCMS: m/z 546 $(M+H)^+$.

ii. Preparation of 4k

[0502] Compound 4k was prepared from aza-T-dCyd (100 mg) and 3k (254 mg, 1.2 Eq.) according to the procedure described for the preparation of 4a. Diastereomer 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.15-8.07 (m, 1H), 7.98-7.87 (m, 1H), 7.71 (q, J=4.6, 4.0 Hz, 1H), 7.59-7.39 (m, 6H), 6.18 (dd, J=12.9, 10.0 Hz, 1H), 6.09 (dd, J=8.1, 6.6 Hz, 1H), 5.42 (d, J=3.9 Hz, 1H), 4.42-4.27 (m, 2H), 4.19 (dt, J=10.7, 6.5 Hz, 1H), 3.93-3.81 (m, 3H), 3.52 (td, J=7.2, 3.0 Hz, 1H), 2.37-2.14 (m, 2H), 1.38 (hept, J=6.0 Hz, 1H), 1.27-1.15 (m, 8H), 0.76 (td, J=7.5, 1.0 Hz, 6H); ^{31}P NMR δ_p 3.63; HR-MS: (M+H) calculated for $C_{27}H_{36}N_5O_7PS.H$ was 606.2146; found 606.2145; HPLC purity=97 (% of AUC), t_R=8.75 minutes. Diastereomer 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.16-8.05 (m, 1H), 8.01-7.88 (m, 1H), 7.80-7.67 (m, 1H), 7.62-7.38 (m, 6H), 6.19 (dd, J=12.8, 10.0 Hz, 1H), 6.09 (dd, J=8.2, 6.5 Hz, 1H), 5.39 (d, J=3.9 Hz, 1H), 4.39-4.25 (m, 2H), 4.10 (dt, J=10.7, 6.8 Hz, 1H), 4.00-3.85 (m, 3H), 3.46 (td, J=7.1, 3.0 Hz, 1H), 2.37 (ddd, J=12.7, 8.2, 4.0 Hz, 1H), 2.21 (ddd, J=13.3, 6.5, 4.1 Hz, 1H), 1.41 (hept, J=6.1 Hz, 1H), 1.28-1.20 (m, 7H), 0.78 (t, J=7.5 Hz, 6H); ^{31}P NMR δ_p 3.72; HR-MS: (M+H) calculated for $C_{27}H_{36}N_5O_7PS.H$ was 606.2146; found 606.2145; HPLC purity=98 (% of AUC), t_R=8.95 minutes.

n. Synthesis of Isopropyl ((((2R,3S,5R)-5-(4-amino-2-oxo-1,3,5-triazin-1(2H)-yl)-3-hydroxytetrahydrothiophen-2-yl)methoxy)(naphthalen-1-yloxy)phosphoryl)-L-alaninate (4l)

[0503]



i. Preparation of Isopropyl ((naphthalen-1-yloxy)(perfluorophenoxy)phosphoryl)-L-alaninate (3l)

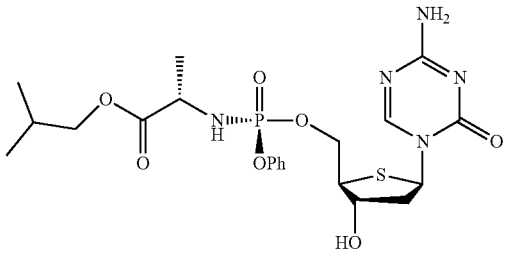
[0504] Intermediate 3l was prepared from 21(5.17 g, 14.5 mmoles, 1.0 Eq.) and pentafluorophenol (2.94 g, 16.0 mmoles, 1.1 Eq.) to afford 1.76 g (24%) of a white solid as a mixture of two diastereomers. 1H NMR (400 MHz, DMSO-d6) δ 8.19-8.08 (m, 1H), 8.06-7.95 (m, 1H), 7.88-7.80 (m, 1H), 7.70-7.48 (m, 4H), 7.08 (ddd, J=23.0, 13.8, 9.9 Hz, 1H), 4.88 (dhept, J=22.8, 6.3 Hz, 1H), 4.16-3.89 (m, 1H), 1.34 (ddd, J=10.9, 7.1, 1.2 Hz, 3H), 1.22-1.06 (m, 6H), 31P NMR δp 0.90 (Diastereomer 1), 0.49 (Diastereomer 2); 19F NMR (400 MHz, DMSO-d6) Of -153.40 to -154.04 (m, 2F), -159.98 to -160.57 (m, 1F), -163.07 (dtd, J=28.0, 23.9, 4.1 Hz, 2F); LCMS: m/z 504 (M+H)+.

ii. Preparation of 4l

[0505] Compound 4l was prepared from aza-T-dCyd (100 mg) and 31(247 mg, 1.2 Eq.) according to the procedure described for the preparation of 4a. Diastereomer 1: ^{1}H NMR (400 MHz, DMSO-d6) δ 8.53 (s, 1H), 8.17-8.03 (m, 1H), 7.94-7.85 (m, 1H), 7.72 (dd, J=5.7, 3.7 Hz, 1H), 7.62-7.30 (m, 7H), 6.15 (dd, J=12.9, 10.0 Hz, 1H), 6.11-6.05 (m, 1H), 5.42 (d, J=3.9 Hz, 1H), 4.80 (hept, J=6.2 Hz, 1H), 4.44-4.27 (m, 2H), 4.19 (dt, J=10.7, 6.5 Hz, 1H), 3.52 (td, J=7.0, 3.0 Hz, 1H), 2.36-2.27 (m, 1H), 2.22 (ddd, J=13.2, 6.6, 4.1 Hz, 1H), 1.22 (d, J=1.1 Hz, 4H), 1.08 (dd, J=7.8, 6.2 Hz, 6H); ^{31}P NMR δ_p 3.60; HR-MS: (M+H) calculated for $C_{24}H_{30}N_5O_7PS.H$ was 564.1676; found 564.1676; HPLC purity=98 (% of AUC), t_R=6.80 minutes. Diastereomer 2: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.19-8.05 (m, 1H), 8.00-7.87 (m, 1H), 7.79-7.66 (m, 1H), 7.64-7.43 (m, 6H), 6.23-6.02 (m, 2H), 5.39 (d, J=3.9 Hz, 1H), 4.85 (hept, J=6.3 Hz, 1H), 4.42-4.29 (m, 2H), 4.11 (dt, J=10.7, 6.8 Hz, 1H), 3.86 (tq, J=10.2, 7.1 Hz, 1H), 3.47 (td, J=7.2, 2.9 Hz, 1H), 2.39 (ddt, J=12.7, 8.3, 4.4 Hz, 1H), 2.22 (ddd, J=13.3, 6.6, 4.1 Hz, 1H), 1.23 (dd, J=7.2, 0.9 Hz, 3H), 1.13 (dd, J=6.3, 1.5 Hz, 6H); ^{31}P NMR δ_p 3.74; HR-MS: (M+H) calculated for $C_{24}H_{30}N_5O_7PS.H$ was 564.1676; found 564.1676; HPLC purity=98 (% of AUC), t_R=7.00 minutes.

o. Synthesis of Isobutyl ((S)-(((2R,3S,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-3-hydroxytetrahydrothiophen-2-yl)methoxy)(phenoxy)phosphoryl)-L-alaninate (5b)

[0506]

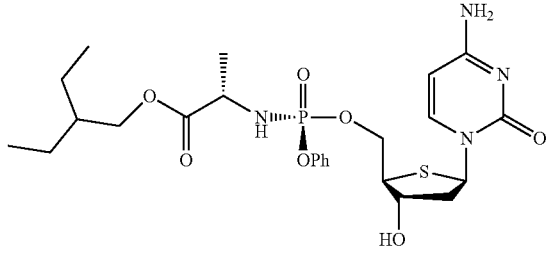


[0507] Compound 5b was prepared from aza-T-dCyd (100 mg) and 3b (222 mg, 1.2 Eq.), according to the procedure described for the preparation of 4a. 1H NMR (400 MHz, DMSO-d6) δ 7.85 (d, J=7.5 Hz, 1H), 7.43-7.28 (m, 2H), 7.22-7.10 (m, 6H), 6.36 (dd, J=8.3, 6.7 Hz, 1H), 6.04 (dd, J=13.2, 10.1 Hz, 1H), 5.74 (d, J=7.4 Hz, 1H), 5.37 (d, J=3.8 Hz, 1H), 4.31 (p, J=3.5 Hz, 1H), 4.19 (ddd, J=10.6, 7.7, 6.4 Hz, 1H), 4.03 (dt, J=10.6, 6.4 Hz, 1H), 3.88-3.71 (m, 4H), 2.13 (ddd, J=8.6, 6.6, 3.5 Hz, 2H), 1.87-1.79 (m, 1H), 1.24 (dd, J=7.1, 0.9 Hz, 3H), 0.86-0.84 (m, 6H); HR-MS: (M+H)

calculated for $C_{22}H_{31}N_4O_7PS.H$ was 527.1724; found 527.1724; 31P NMR Op 3.20; HPLC purity=97 (% of AUC), t_R=16.62 minutes.

p. Synthesis of 2-Ethylbutyl ((S)-(02R,3S,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-3-hydroxytetrahydrothiophen-2-yl)methoxy)(phenoxy)phosphoryl)-L-alaninate (5c)

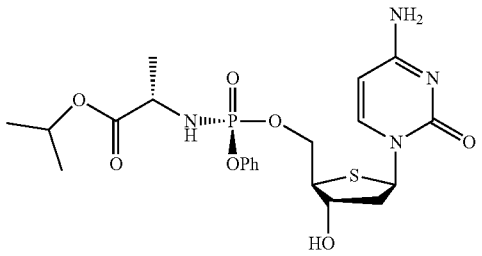
[0508]



[0509] Compound 5c was prepared from aza-T-dCyd (100 mg) and 3c (244 mg, 1.2 Eq.) according to the procedure described for the preparation of 4a. 1H NMR (400 MHz, DMSO-d6) δ 7.85 (d, J=7.5 Hz, 1H), 7.35 (tt, J=7.4, 2.2 Hz, 2H), 7.22-7.10 (m, 5H), 6.35 (dd, J=8.4, 6.7 Hz, 1H), 6.03 (dd, J=13.1, 10.1 Hz, 1H), 5.74 (d, J=7.4 Hz, 1H), 5.37 (d, J=3.7 Hz, 1H), 4.31 (p, J=3.5 Hz, 1H), 4.19 (ddd, J=10.7, 7.7, 6.4 Hz, 1H), 4.02-3.79 (m, 4H), 3.42 (dd, J=4.7, 2.8 Hz, 2H), 2.20-2.04 (m, 2H), 1.43 (dp, J=12.6, 6.3 Hz, 1H), 1.29-1.19 (m, 7H), 0.82 (dd, J=7.4, 2.6 Hz, 6H); HR-MS: (M+H) calculated for $C_{24}H_{35}N_4O_7PS.H$ was 555.2037; found 555.2036; 31P NMR δp 3.20; HPLC purity=99 (% of AUC), t_R=20.0 minutes.

q. Synthesis of Isopropyl ((S)-(02R,3S,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-3-hydroxytetrahydrothiophen-2-yl)methoxy)(phenoxy)phosphoryl)-L-alaninate (5d)

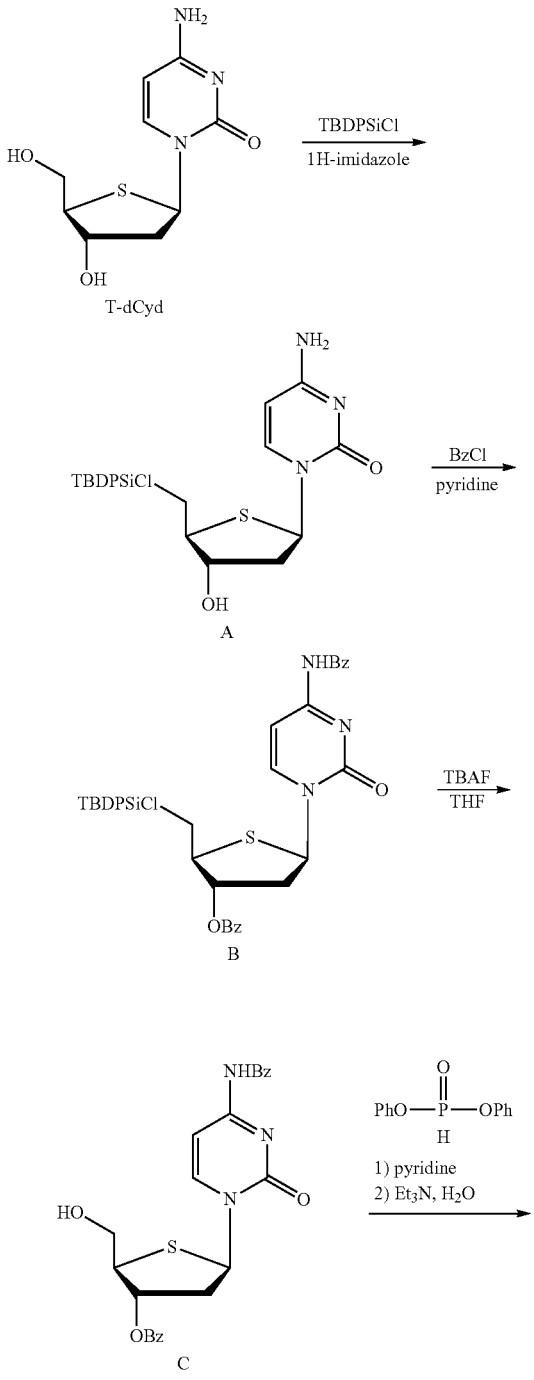
[0510]



[0511] Compound 5d was prepared from aza-T-dCyd (100 mg) and 3d (222 mg, 1.2 Eq.) according to the procedure described for the preparation of 4a. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (d, J=7.5 Hz, 1H), 7.40-7.31 (m, 2H), 7.25-7.08 (m, 6H), 6.36 (dd, J=8.3, 6.8 Hz, 1H), 6.00 (dd, J=13.2, 10.0 Hz, 1H), 5.80-5.67 (m, 1H), 5.37 (d, J=3.8 Hz, 1H), 4.85 (dq, J=12.6, 6.3 Hz, 1H), 4.32 (q, J=3.5 Hz, 1H), 4.19 (ddd, J=10.6, 7.7, 6.4 Hz, 1H), 4.10-3.98 (m, 1H), 3.86-3.67 (m, 1H), 3.43 (ddd, J=8.2, 5.9, 2.6 Hz, 1H), 2.13 (dt, J=8.7, 4.0 Hz, 2H), 1.21 (dd, J=7.1, 0.9 Hz, 4H), 1.18-1.08 (m, 9H); HR-MS: (M+H) calculated for $C_{21}H_{29}N_4O_7PS.H$ was 513.1567; found 513.1571; ^{31}P NMR δ_p 3.13; HPLC purity=94 (% of AUC), t_R=16.05 minutes.

r. Synthesis of ((2R,3S,5R)-5-(4-amino-2-oxopyrimidin-1(2H)-yl)-3-hydroxytetrahydrothiophen-2-yl)methyl Dihydrogen Phosphate (16: SRI-43590)

[0512]



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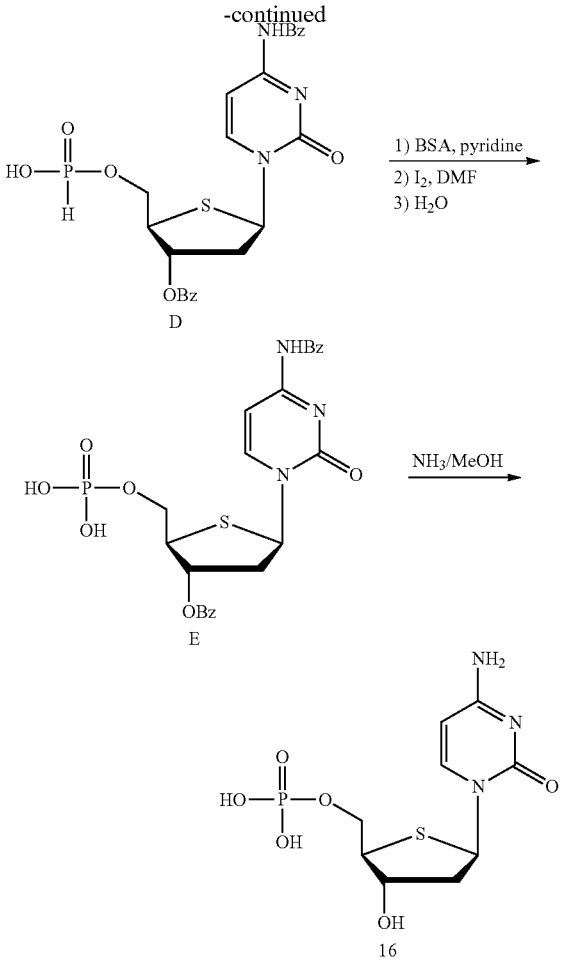


i. Preparation of 4-amino-1-((2R,4S,5R)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-4-hydroxytetrahydrothiophen-2-yl)pyrimidin-2(1H)-one (A)

[0513] A solution of 4-amino-1-[(2R,4R,5R)-4-hydroxy-5-(hydroxymethyl)thiolan-2-yl]pyrimidin-2-one (130.0 mg, 0.534 mmol) T-dCyd, tert-butyl(chloro)diphenylsilane (190.0 mg, 0.691 mmol) and imidazole(94.0 mg, 1.38 mmol) in DMF (2 mL) was stirred at room temperature for 2.5 h. The reaction mixture was diluted with 20 mL H_2O and was extracted with EtOAc (40 mL×3). The organic layers were combined and washed with brine (50 mL×3). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to afford 330 mg (crude) of 4-amino-1-[(2R,4R,5R)-5-[[(tert-butyldiphenylsilyl)oxy]methyl]-4-hydroxythiolan-2-yl]pyrimidin-2-one A. It was used in the next step without further purification. LCMS $[M+1]^+$=482.

ii. Preparation of (2R,3S,5R)-5-(4-benzamido-2-oxopyrimidin-1(2H)-yl)-2-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydrothiophen-3-yl Benzoate (B)

[0514] To a solution of 4-amino-1-[(2R,4R,5R)-5-[[(tert-butyldiphenylsilyl)oxy]methyl]-4-hydroxythiolan-2-yl]pyrimidin-2-one A (330.0 mg, crude) in pyridine (2 mL) was added benzoyl chloride (260.0 mg, 1.85 mmol) at 0° C. The resulting solution was stirred at room temperature for 1.5 h. The resulting solution was diluted with 50 mL H_2O and extracted with EtOAc (40 mL×3). The organic layers were combined and dried over anhydrous sodium sulfate. The solvent was concentrated under vacuum and the residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (60%-80%) to afford 280 mg of (2R,3R,5R)-5-(4-benzamido-2-oxopyrimidin-1-yl)-2-[[(tert-butyldiphenylsilyl)oxy]methyl]thiolan-3-yl benzoate B as a white solid. LCMS$[M+1]^+$=690.

iii. Preparation of (2R,3S,5R)-5-(4-benzamido-2-oxopyrimidin-1(2H)-yl)-2-(hydroxymethyl)tetrahydrothiophen-3-yl Benzoate (C)

[0515] To a solution of (2R,3R,5R)-5-(4-benzamido-2-oxopyrimidin-1-yl)-2-[[(tert-butyldiphenylsilyl)oxy]methyl]thiolan-3-yl benzoate B (280.0 mg, 0.405 mmol) in THF (2 mL) was added a solution of TBAF in THF (1 M, 0.8 mL) at room temperature. The solution was stirred at room temperature for 1 h. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (30 mL×3). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (~98%) to afford 150 mg of (2R,3R,5R)-5-(4-benzamido-2-oxopyrimidin-1-yl)-2-(hydroxymethyl)thiolan-3-yl benzoate C as a white solid. LCMS[M+1]+=452. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.30 (s, 1H), 8.62 (d, J=7.6 Hz, 1H), 8.02 (dd, J=7.5, 2.1 Hz, 4H), 7.72 (t, J=7.4 Hz, 1H), 7.67-7.48 (m, 5H), 7.44 (d, J=7.5 Hz, 1H), 6.48 (t, J=7.6 Hz, 1H), 5.79-5.68 (m, 1H), 5.38 (t, J=5.3 Hz, 1H), 3.73 (dt, J=7.9, 4.3 Hz, 3H), 2.65 (td, J=9.4, 8.2, 3.5 Hz, 2H).

iv. Preparation of (2R,3S,5R)-5-(4-benzamido-2-oxopyrimidin-1(2H)-yl)-2-(((hydroxyhydrophosphoryl)oxy)methyl)tetrahydrothiophen-3-yl Benzoate (D)

[0516] To a solution of (2R,3R,5R)-5-(4-benzamido-2-oxopyrimidin-1-yl)-2-(hydroxymethyl)thiolan-3-yl benzoate C (130.0 mg, 0.288 mmol) in pyridine (1 mL) was added diphenyl phosphonate (336.0 mg, 1.435 mmol) at 0° C. The reaction was stirred at room temperature for 2 h. Then a solution of Et_3N (0.2 mL) and H2O 2O (0.2 mL) was added at 0° C. and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was concentrated under vacuum. The residue was purified by reverse phase Flash chromatography (0-100% CH_3CN in H_2O (0.05% NH_4HCO_3)) to afford 105 mg of [(2R,3R,5R)-5-(4-benzamido-2-oxopyrimidin-1-yl)-3-(benzoyloxy)thiolan-2-yl]methoxyphosphinic acid D as a white solid. LCMS[M+1]+=516.

V. Preparation of (2R,3S,5R)-5-(4-benzamido-2-oxopyrimidin-1(2H)-yl)-2-((phosphonooxy)methyl)tetrahydrothiophen-3-yl Benzoate (E)

[0517] To a solution of [(2R,3R,5R)-5-(4-benzamido-2-oxopyrimidin-1-yl)-3-(benzoyloxy)thiolan-2-yl]methoxyphosphinic acid D (105.0 mg, 0.205 mmol) in pyridine (1.5 mL) was added N,O-Bis(trimethylsilyl)acetamide (207.0 mg, 1.02 mmol) at 0° C. and stirred at room temperature for 0.5 h. Then a solution of 12 in DMF (0.6 M, 0.34 mL) was added at 0° C. and the resulting solution was stirred at room

temperature for 0.5 h. Then H2O 2O (0.36 mL) was quickly injected into the reaction mixture and stirred at room temperature for 0.5 h. The residue was purified by reverse phase Flash chromatography (0-100% CH_3CN in H_2O (0.05% NH_4HCO_3)) to afford 60 mg of [(2R,3R,5R)-5-(4-benzamido-2-oxopyrimidin-1-yl)-3-(benzoyloxy)thiolan-2-yl] methoxyphosphonic acid E as a white solid. LCMS$[M+1]^+$ =482.

vi. Preparation of 16

[0518] A solution of [(2R,3R,5R)-5-(4-benzamido-2-oxopyrimidin-1-yl)-3-(benzoyloxy)thiolan-2-yl]methoxyphosphonic acid E (60.0 mg, 0.112 mmol) in 7M NH_3/MeOH (1 mL) was stirred at room temperature for 20 h. The solution was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep Amide OBD Column, 19A-150 mm Sum 13 nm; Mobile Phase A:Water (10 MMOL/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate: 25 mL/min; Gradient: 95 B to 70 B in 9 min; 254/220 nm; RT1:8.6;) to afford 16.1 mg of [(2R,3R,5R)-5-(4-amino-2-oxopyrimidin-1-yl)-3-hydroxythiolan-2-yl] methoxyphosphonic acid 16 as a white solid. LCMS$[M+1]^+$ =324. ^1H NMR (300 MHz, D_2O) δ 8.24 (d, J=7.7 Hz, 1H), 6.26 (t, J=7.1 Hz, 1H), 6.07 (d, J=7.7 Hz, 1H), 4.54 (q, J=4.2 Hz, 1H), 4.10-3.88 (m, 2H), 3.55 (q, J=4.8 Hz, 1H), 2.52-2.35 (m, 1H), 2.30-2.15 (m, 1H).

[0519] 2. Biology Experimentals

[0520] a. Cell Viability Assay

[0521] KG1a (CCL-246.1, ATCC) and CCRF-CEM (CCL-199, ATCC) cells were grown in RPMI-1640 media containing 10% FBS in T-75 flasks to a density of 1×10^6 cells per mL. Exponentially gown cells were used for the assay. Day 1: 7.5×10^3 cells were seeded in each well of 96 well plate. Day 2: Cells were treated with serial dilutions of each compound (starting 20 uM) or with DMSO as control for 72 hours. Day 5: CellTiter Glo (G9241, Promega) was added to the media of each well and measured by plate reader (Synergy 4, Biotek). Data analysis: Using GraphPad Prism 7 (GraphPad).

[0522] b. Western Blot Analysis

[0523] Cells were treated with serial dilutions of each compound (starting 100 uM for HCT-116 and NCI-H23 cells, and 20 uM for KG-1a and CCRF-CEM cells) or with DMSO as control for 96 hours. Cell lysates were collected and proteins were separated with a SDS-PAGE gel, transferred to a nitrocellulose membrane, blocked in 5% non-fat milk in TBS-T, and probed with anti DNMT-1 (1:7000) rabbit polyclonal antibodies (cat #ab19905, Abcam) in 5% non-fat milk in TBS-T overnight. Membranes were washed three times with TBS-T. The anti-rabbit IgG (7074p2, Cell Signaling) secondary antibody was added at a concentration of 1:5000 in 5% non-fat milk in TBS-T for two hours in room temperature. Membranes were then washed three times with TBS-T, 5 minutes each time. Membranes were then incubated with SuperSignal West Pico Chemiluminescent Substrate (#34080 Thermo) and exposed onto film. Membranes were stripped with stripping buffer (#21059, Thermo) and re-probed with mouse anti tubulin 1:10,000 (T9026, Sigma) and anti-mouse IgG 1:5,000 (70'76p2, Cell Signaling).

[0524] c. Cytidine Deaminase Activity

[0525] 77.5×10^3 cells/well were plated in a 96 well plate in duplicate. Tetrahydrouridine (THU), a Cytidine Deaminase inhibitor was dosed at 1:5 10-point serial dilution, with a top dose of 100 μM, as a control. Compound 2 and Aza-T-dCyd were dosed at a 1:5 10-point serial dilution with a top dose of 20 μM in the presence of 20 μM THU. Cells were cultured in the presence of compound for 72 hours and then assayed by cell titer glow for viability.

[0526] d. Deoxycytidine Kinase Activity

[0527] 7.5×10^3 cells/well were plated in a 96 well plate in duplicate. Either compound 2 and Aza-T-dCyd were dosed at a 1:5 10-point serial dilution with a top dose of 5 μM in the presence of 20 μM 2-Deoxycytidine (dCyd, Sigma Cat #: D3897, CAS 951-77-9), a deoxycytidine kinase inhibitor. Cells were cultured in the presence of compound for 72 hours. CellTiter Glo (G9241, Promega) was added to the media of each well and measured by a plate reader (Synergy 4, Biotek). The results were analyzed by GraphPad Prism 7 (GraphPad).

[0528] e. Nucleoside Transporter (hENT-1) Activity

[0529] 7.5×10^3 cells/well were plated in a 96 well plate in duplicate. Either compound 2 and Aza-T-dCyd were dosed at a 1:5 10-point serial dilution with a top dose of 5 μM in the presence of 5 μM Dipyridamole (DPD, Sigma Cat #: D9766 CAS 58-32-2), a hENT-1 inhibitor. Cells were cultured in the presence of compound for 72 hours. CellTiter Glo (G9241, Promega) was added to the media of each well and measured by a plate reader (Synergy 4, Biotek). The results were analyzed by GraphPad Prism 7 (GraphPad).

[0530] 3. Characterization of 4'-thio-nucleotide and Nucleoside Analogs

[0531] A list of compounds evaluated for anti-cancer activity is shown in Table 1 below.

TABLE 1

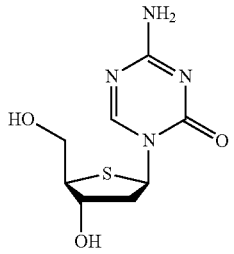
No.	Structure
Aza-T-dCYd	

TABLE 1-continued

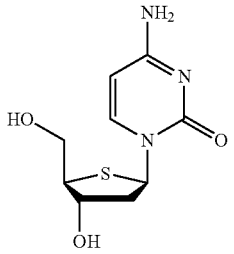
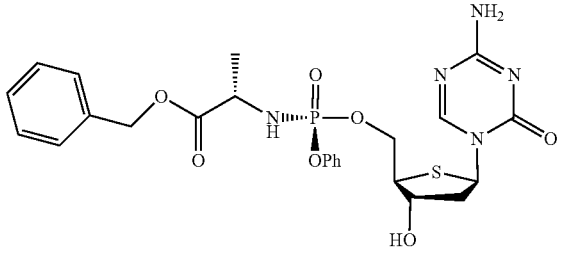
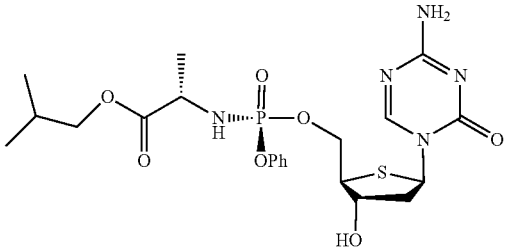
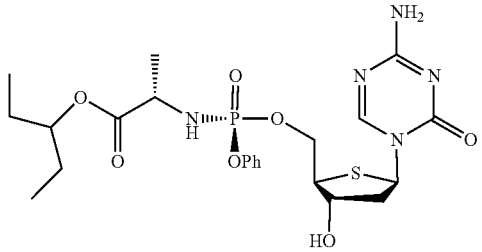
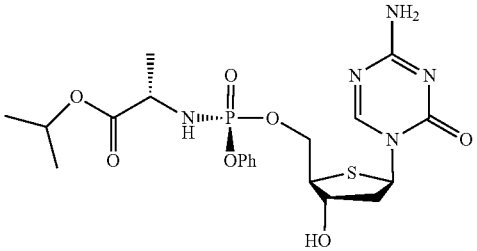
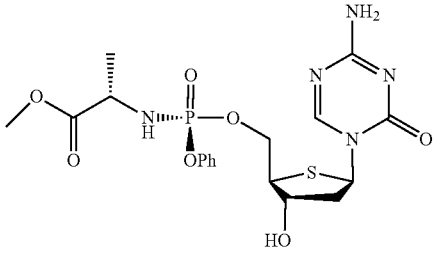
No.	Structure
T-dCyd	
1	
2	
3	
4	
5	

TABLE 1-continued

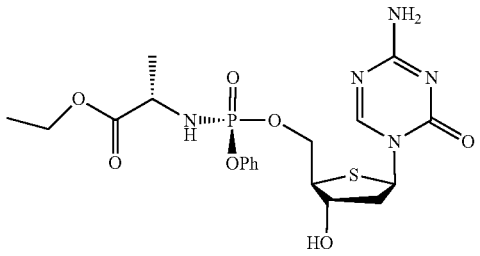
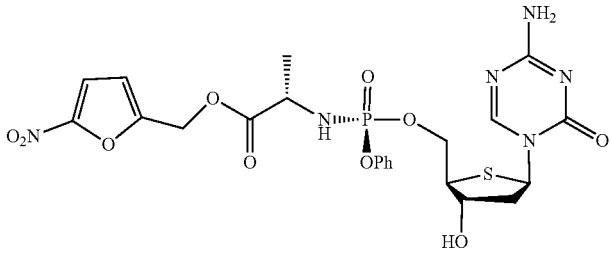
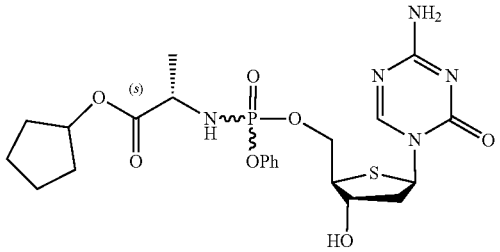
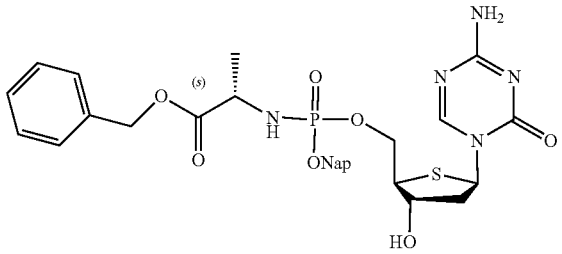
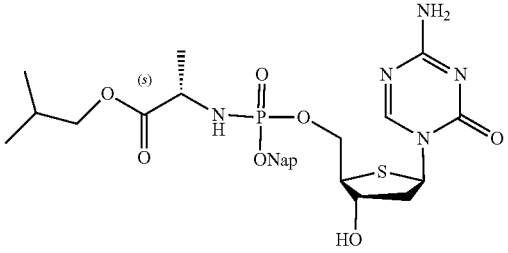
No.	Structure
6	
7	
8 (Diastereomers 1 & 2)	 (S,S_P) and (S,R_P) as single diastereomers
9 (Diastereomers 1 & 2)	 (S,Sp) and (S,Rp) as single diastereomers
10 (Diastereomers 1 & 2)	 (S,Sp) and (S,Rp) as single diastereomers

TABLE 1-continued

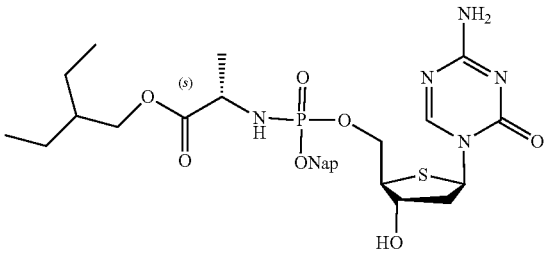
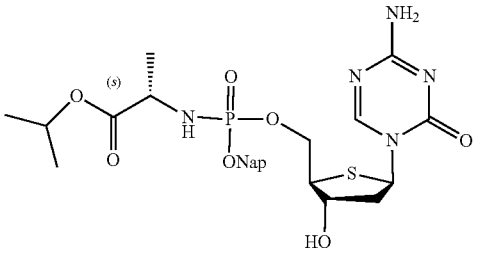
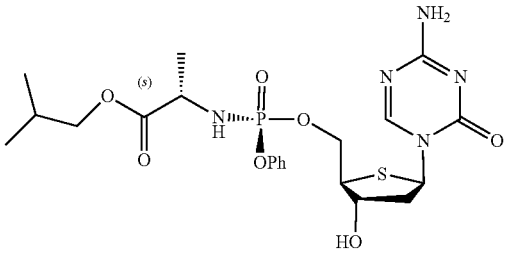
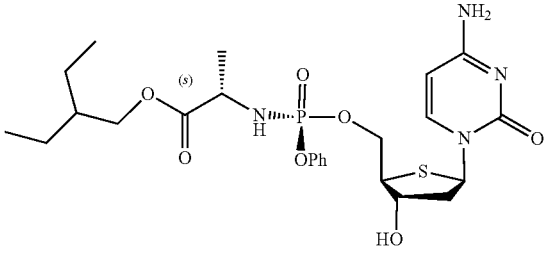
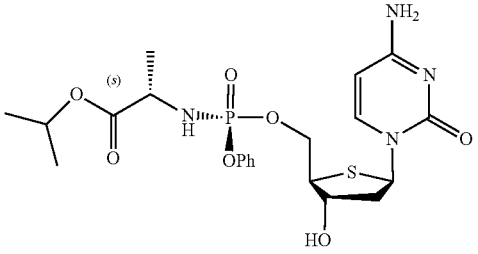
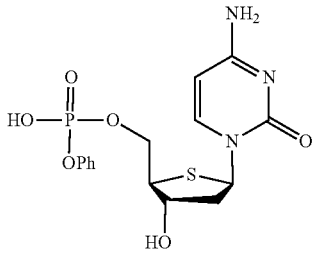
No.	Structure
11 (Diastereomers 1 & 2)	 (S,Sp) and (S,Rp) as single diastereomers
12 (Diastereomers 1 & 2)	 (S,Sp) and (S,Rp) as single diastereomers
13	
14	
15	

TABLE 1-continued

No.	Structure
16	

[0532] 4. Anti-Cancer Activity of 4'-thio-nucleotide and Nucleoside Analogs

[0533] The activity of the compounds in various cell lines is illustrated in FIG. **1**A-D (KG-1 cells) and FIG. **2**A-D (CEM cells), and in Table 2 below.

TABLE 2

No.	Cell Line IC_{50} (μM) KG-1a	Cell Line IC_{50} (μM) CEM	CEM-DNMT-1 IC_{50} (μM)
Aza-T-dCyd	0.03	0.03	0.38
1	0.92	0.13	1.2
2	1.34	0.24	0.8
3	1.5	0.16	0.62
4	0.57	0.24	0.85
5	1.67	2.06	0.61
6	0.31	1.73	0.35
7	0.76	1.71	0.22
8 Diastereomer 1	0.6	2.08	0.33
Diastereomer 2	1.04	1.65	0.45
9 Diastereomer 1	1.1	0.5	0.3
Diastereomer 2	0.4	0.2	1.4
10 Diastereomer 1	0.3	0.2	0.6
Diastereomer 2	0.3	0.2	0.8
11 Diastereomer 1	0.6	0.2	0.5
Diastereomer 2	0.6	0.08	0.5
12 Diastereomer 1	0.6	0.3	0.8
Diastereomer 2	0.7	0.1	1.0
T-dCyd (7529)	0.48	0.08	0.47
13 (41760)	0.65	0.13	0.64
14 (41761)	0.62	0.15	1.0
15 (40650)	0.9	0.37	0.33
16 (43590)	0.18	0.22	0.17

[0534] 4. Effect of hENT-1 Transporter on Nucleotide 3 and its Parent Drug Aza-T-dCYD

[0535] Table 3 below shows representative data illustrating the effect of hENT-1 transporter on nucleotide 3 and its parent drug Aza-T-dCyd (hENT Inhibitor: Dipyridamole (DPD)). Without wishing to be bound by theory, compound 3 does not significantly rely on hENT-1 to enter the cancer cells and exert its anticancer effect.

TABLE 3

Compound	CEM IC_{50} (μM) Without DPD	CEM IC_{50} (μM) With DPD (5 μM)
Aza-T-dCyd	0.03	>3
3	0.35	3.1

[0536] 5. Effect of Cytidine Deaminase (CDA) on Nucleotide 3 and its Parent Aza-T-dCYD

[0537] Table 4 below shows representative data illustrating the effect of CDA on Nucleotide 3 and its parent Aza-T-dCyd (CDA inhibitor: tetrahydrouridine (THU)). Without wishing to be bound by theory, compound 3 did overcome CAD comparing to its parent drug.

TABLE 4

Compound	HCT-116 IC_{50} (μM) Without THU	HCT-116 IC_{50} (μM) With THU (20 μM)
Aza-T-dCyd	7	0.7
3	8	12

[0538] 6. Effect of Deoxycytidine Kinase (DCK) Activation on Nucleotide 3 and its Parent Aza-T-dCYD

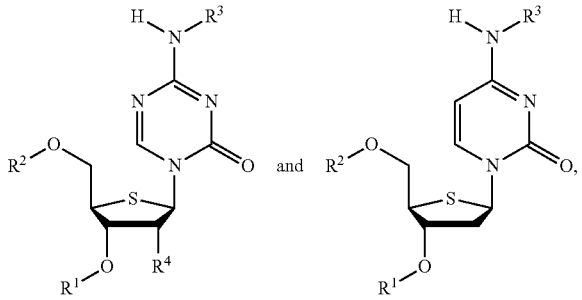
[0539] Table 5 below shows representative data illustrating the effect of dCK activation on Nucleotide 3 and its parent Aza-T-dCyd (dCK Inhibitor: 2'-deoxycytidine (dCyd)). Without wishing to be bound by theory, compound 3 does not rely on dCK activation comparing to its parent drug.

TABLE 5

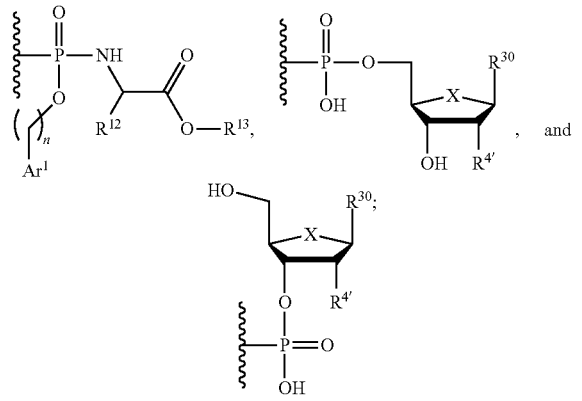
Compound	CEM IC_{50} (μM) Without dCyd	CEM IC_{50} (μM) With dCyd (20 μM)
Aza-T-dCyd	0.03	19
3	0.3	6.5

[0540] It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

1. A compound having a structure represented by a formula selected from:



wherein each of R^1 and R^2 is independently selected from hydrogen, —C(O)R^{10}, —P(O)(OR^{11})$_2$, —P(O)(OH)OP(O)(OH)OP(O)(OH)$_2$, and a structure represented by a formula selected from:



provided that one of R^1 and R^2 is hydrogen;

wherein n is selected from 0, 1, and 2;

wherein X, when present, is selected from O and S;

wherein R^{10}, when present, is selected from C1-C30 alkyl, C2-C30 alkenyl, and —CH(NH_2)R^{20};

wherein R^{20}, when present, is selected from hydrogen, methyl, isopropyl, isobutyl, sec-butyl, —$(CH_2)_3NHC(NH)NH_2$, —$(CH_2)_4NH_2$, —CH_2CO_2H, —$(CH_2)_2CO_2H$, —CH_2OH, —CH(OH)CH_3, —$CH_2C(O)NH_2$, —$(CH_2)_2C(O)NH_2$, —CH_2SH, —$(CH_2)_2SCH_3$, —CH_2SeH, —$CH_2C_6H_5$, and CH_2Cy^1;

wherein Cy^1, when present, is selected from monocylic aryl, para-hydroxy monocyclic aryl, 4-imidazolyl, and 3-indolyl;

wherein each occurrence of R^{11}, when present, is independently selected from hydrogen, —(C1-C10 alkyl)CO_2(C1-C10 alkyl), —(C1-C10 alkoxy)CO_2(C1-C10 alkyl), —(C1-C10 alkyl)CO_2(C1-C10 alkylthio), —(C1-C10 alkyl)-S—S—(C1-C10 alkyl), and Ar^2, and wherein each alkyl is substituted with 0, 1, 2, or 3 groups independently selected from halogen and OH;

wherein Ar^2, when present, is selected from aryl and heteroaryl substituted with 1 or 2 groups independently selected from C1-C10 alkyl and nitro;

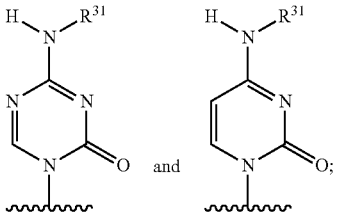
wherein R^{12}, when present, is selected from hydrogen, C1-C8 alkyl, C1-C8 hydroxyalkyl, C1-C8 alkylamino, (C1-C8)C(O)NH_2, aryl, and —(CH_2)aryl;

wherein R^{13}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and Ar^3;

wherein Ar^3, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C10 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino;

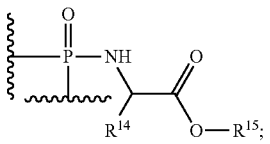
wherein Ar^1, when present, is selected from aryl and heteroaryl and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, —OH, —NH_2, —NO_2, —CN, C1-C4 alkyl, C1-C4 haloalkyl, C1-C4 alkoxy, C1-C4 hydroxy, C1-C4 aminoalkyl, C1-C4 alkylamino, and (C1-C4)(C1-C4) dialkylamino;

wherein R^{30}, when present, is a structure selected from:



wherein R^{31}, when present, is selected from hydrogen, —C(O)(C1-C30 alkyl), and —C(O)(C2-C30 alkenyl);

or wherein each of R^1 and R^2 together comprise a structure represented by a formula:



wherein R^{14}, when present, is C1-C8 alkyl;

wherein R^{15}, when present, is selected from C1-C10 alkyl, C3-C10 cycloalkyl, and aryl substituted with 0 or 1 C1-C10 alkyl groups;

wherein R^3 is selected from hydrogen, —C(O)(C1-C30 alkyl), and —C(O)(C2-C30 alkenyl);

wherein each of R^4 and $R^{4'}$, when present, is independently selected from hydrogen, fluoro, —CN, C2-C4 alkenyl, C2-C4 alkynyl, C1-C4 haloalkyl, and —OR^{16}; and

wherein R^{16}, when present, is selected from hydrogen, methyl, and —C(O)R^{10},

provided that R^1, R^2, and R^3 are not simultaneously hydrogen,

or a pharmaceutically acceptable salt thereof.

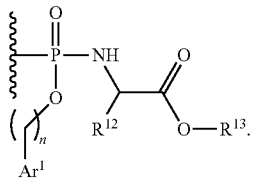
2. The compound of claim **1**, wherein R^1 is hydrogen.

3. The compound of claim 3, wherein R^2 is hydrogen.

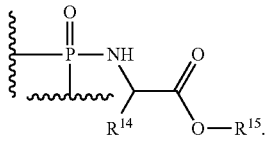
4. The compound of claim 3, wherein R^2 is —C(O)R^{10}.

5. The compound of claim 3, wherein R^2 is —P(O)(OR^{11})$_2$.

6. The compound of claim 3, wherein R^2 is a structure represented by a formula:

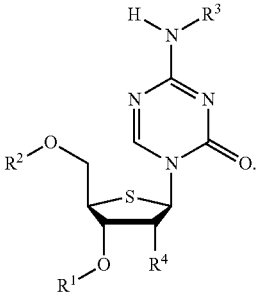


7. The compound of claim 1, wherein each of R^1 and R^2 together comprise a structure represented by a formula:

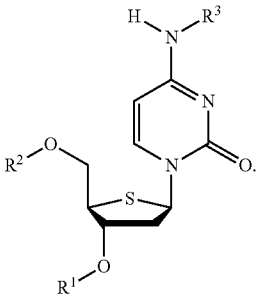


8-12. (canceled)

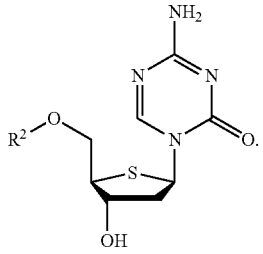
13. The compound of claim 1, wherein the compound has a structure represented by a formula:



14. The compound of claim 1, wherein the compound has a structure represented by a formula:

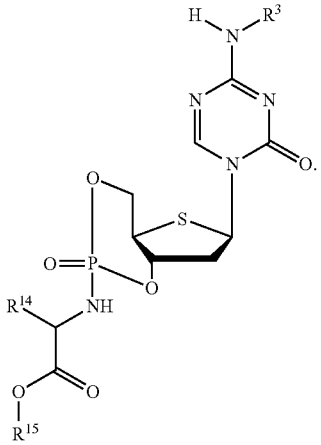


15. The compound of claim 1, wherein the compound has a structure represented by a formula:



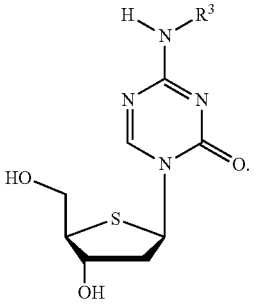
16-19. (canceled)

20. The compound of claim 1, wherein the compound has a structure represented by a formula:



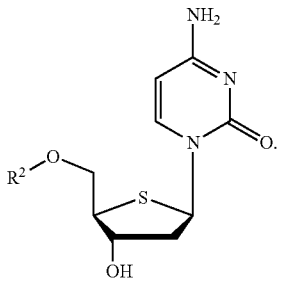
21. (canceled)

22. The compound of claim 1, wherein the compound has a structure represented by a formula:



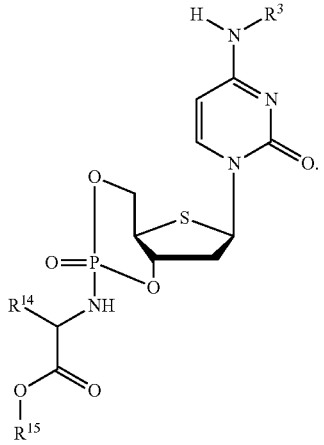
23. (canceled)

24. The compound of claim **1**, wherein the compound has a structure represented by a formula:



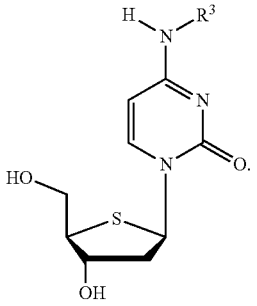
25-28. (canceled)

29. The compound of claim **1**, wherein the compound has a structure represented by a formula:



30. (canceled)

31. The compound of claim **1**, wherein the compound has a structure represented by a formula:



32. (canceled)

33. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim **1** and a pharmaceutically acceptable carrier.

34. A method of treating a disorder of uncontrolled cellular proliferation in a subject, the method comprising the step of administering to the subject an effective amount of the compound of claim **1**.

35-40. (canceled)

41. The method of claim **0**, wherein the disorder is a cancer.

42. The method of claim **35-40**, wherein the cancer is selected from a sarcoma, a carcinoma, a hematological cancer, a solid tumor, breast cancer, cervical cancer, gastrointestinal cancer, colorectal cancer, brain cancer, skin cancer, prostate cancer, ovarian cancer, bladder cancer, thyroid cancer, testicular cancer, pancreatic cancer, endometrial cancer, melanoma, glioma, leukemia, lymphoma, chronic myeloproliferative disorder, myelodysplastic syndrome, myeloproliferative neoplasm, and plasma cell neoplasm (myeloma).

43. (canceled)

44. The method of claim **35-40**, wherein the cancer is a liver cancer.

45-70. (canceled)

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